

1 UNITED STATES DISTRICT COURT  
2 DISTRICT OF NEVADA  
3 BEFORE THE HONORABLE MIRANDA DU, DISTRICT JUDGE  
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4 AMARIN PHARMA, INC., and :  
5 AMARIN PHARMACEUTICALS :  
6 IRELAND LIMITED, :  
7 : No. 2:16-cv-02525-MMD-NJK  
8 Plaintiffs, :  
9 : January 13, 2020  
10 -vs- :  
11 : Reno, Nevada  
12 HIKMA PHARMACEUTICALS USA :  
13 INC., et al., : Volume 1  
14 Defendants. :  
15 \_\_\_\_\_ :

16 TRANSCRIPT OF BENCH TRIAL

17 APPEARANCES:

18 FOR THE PLAINTIFFS: MEAGAN P. KEANE, CHRISTOPHER N.  
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24 Official Reporter  
25 U.S. District Court  
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(Appearances continue on next page.)

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08:37:38

1 RENO, NEVADA, MONDAY, JANUARY 13, 2020, 8:30 A.M.

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08:32:45 3  
08:32:45 4 THE CLERK: 2:16-cv-2525-MMD-NJK, Amarin Pharma  
08:33:33 5 versus Hikma and Dr. Reddy's Laboratories.

08:36:51 6 Your Honor, present for plaintiffs, counsel  
08:36:55 7 Megan Keane, Chris Sipes, Michael Kennedy, Jeff Elikan, Joe  
08:37:08 8 Kennedy, Alaina Whitt, Barbara Kurys, Han Park, Daniel  
08:37:17 9 Farnoly, and Eric Sonnenschein.

08:37:20 10 Present for Defendant Hikma, Charles Klein,  
08:37:25 11 Eimeric Reig, West Allen, Claire Fundakowski, and Alison  
08:37:32 12 Heydorn.

08:37:35 13 Present for Dr. Reddy's Laboratories Connie  
08:37:39 14 Huttner, Michael Rounds, and James Barabas.

08:37:42 15 Your Honor, also present are two litigation  
08:37:46 16 technology personnel.

08:37:48 17 Present for Amarin as general counsel and  
08:37:51 18 corporate representative is Joe Kennedy. Present for Hikma  
08:37:58 19 defendants is Neema Kumar, and present as in-house counsel for  
08:38:03 20 DRL are Andrew Ellen and Deepth Jain.

08:38:11 21 THE COURT: All right. Good morning, everyone.

08:38:13 22 I think we should begin with the brief openings  
08:38:18 23 that I agreed to permit counsel to do. After openings, I'll  
08:38:22 24 address briefly the -- well, I can address it now.

08:38:26 25 The parties filed stipulated facts which I have

08:38:29 1 approved. There are 234 stipulated facts. So when you refer  
08:38:33 2 to the stipulated facts, I would ask that you refer to the  
08:38:35 3 number for the record, and then there's also stipulated  
08:38:39 4 admitted exhibits which, for the record, I will admit as well.  
08:38:43 5 It's ECF number 325.

08:38:46 6 So when you reference exhibits that have been  
08:38:50 7 stipulated to, I would ask you do that as well for the record.

08:38:53 8 And then for my benefit, I know that counsel  
08:38:56 9 used an abbreviation for triglyceride which is TG, but I think  
08:39:03 10 we should come up with an abbreviation for  
08:39:06 11 hypertriglyceridemia so that I don't have to say it every  
08:39:12 12 time. Would HGTD -- would that suffice?

08:39:17 13 MR. SIPES: Your Honor, what we've seen a lot  
08:39:19 14 used as abbreviations for hypertriglyceridemia, HTG, severe  
08:39:27 15 hypertriglyceridemia, SHGT, or sometimes it's referred to as  
08:39:31 16 very high triglycerides which is VHTG.

08:39:36 17 THE COURT: So for the one I've seen used in  
08:39:39 18 this case most frequently is HTG, hypertriglyceridemia.

08:39:47 19 MR. SIPES: HGT.

08:39:47 20 THE COURT: HTG. All right. So we'll use HTG.

08:39:49 21 Thank you. Let's proceed.

08:39:51 22 MR. SIPES: Your Honor, one other thing -- this  
08:39:53 23 is Christopher Sipes for Amarin. There's a few preliminary  
08:39:57 24 matters we're hoping to address before opening statements if I  
08:39:59 25 could, Your Honor.

08:40:00 1 One, a number of exhibits have portions that are  
08:40:04 2 confidential or proprietary so we just for now ask for time  
08:40:09 3 for redactions after admission before they're published to the  
08:40:12 4 public. So we would appreciate that, Your Honor.

08:40:15 5 THE COURT: Well, and I also -- I think what  
08:40:18 6 would make sense sometime today -- and if I don't need to  
08:40:23 7 resolve it in the morning, I prefer to do it in the afternoon,  
08:40:28 8 and that is how the -- process for presenting testimony on  
08:40:32 9 sealed -- on sealed testimony basically.

08:40:36 10 And you saw the order that I issued last Friday  
08:40:39 11 that I would be very carefully reviewing what the parties  
08:40:42 12 designated as confidential because, quite frankly, I don't  
08:40:46 13 find that a lot of information is now proprietary.

08:40:51 14 So I want to give you a chance to explain, and I  
08:40:53 15 thought we would do it end at the of the day. It's really  
08:40:57 16 cumbersome for the Court to seal the entire courtroom every  
08:41:00 17 time there's reference to sealed testimony.

08:41:02 18 So if there's a way to arrange it, whoever is  
08:41:05 19 testifying can offer the sealed testimony towards the end,  
08:41:09 20 otherwise I would have to ask everyone who is not a party or  
08:41:12 21 counsel to leave the courtroom, lock the courtroom, seal that  
08:41:16 22 portion of the testimony, and then unseal and start over  
08:41:19 23 again.

08:41:19 24 MR. SIPES: Your Honor, we don't anticipate  
08:41:22 25 needing to seal the courtroom today. So I think we can put

08:41:26 1 that off. We can -- at least on our side.

08:41:28 2 THE COURT: Well, does that mean that the  
08:41:30 3 testimony offered by the expert that you previously designated  
08:41:35 4 as sealed will now no longer be sealed if I don't seal the  
08:41:38 5 courtroom?

08:41:39 6 MR. SIPES: I think in terms of the testimony  
08:41:40 7 that we're anticipating coming in today, that would not be  
08:41:44 8 confidential that would need to be sealed.

08:41:45 9 THE COURT: Then we can address the issue of  
08:41:47 10 sealing at the end of the today.

08:41:48 11 MR. SIPES: That's what I believe, Your Honor.

08:41:50 12 The parties also have worked out the process for  
08:41:53 13 the submission of deposition designations if it's permissible  
08:41:58 14 with the Court.

08:41:58 15 The parties would submit a list of the parties'  
08:42:01 16 deposition designations, counterdesignations and rebuttal  
08:42:01 17 designations. I can find the page and line numbers. This  
08:42:09 18 submission will be considered submission of the testimony into  
08:42:10 19 evidence at that time.

08:42:11 20 At the same time the exhibits associated with  
08:42:14 21 such testimony will be moved into evidence. At the end of the  
08:42:18 22 trial the parties will submit thumb drives containing  
08:42:22 23 hyperlinked versions of the deposition transcript with the  
08:42:25 24 respective parties' designations highlighted in different  
08:42:26 25 colors, and the exhibits will be hyperlinked for the Court's

08:42:30 1 convenience. So we'll move it in in a timely fashion, but  
08:42:33 2 we'll actually give the Court the electronic versions of the  
08:42:37 3 actual testimony and exhibits at the end.

08:42:38 4 THE COURT: And you're giving me not just the  
08:42:40 5 video depositions but the written transcript as well?

08:42:43 6 MR. SIPES: That's my understanding, your Honor,  
08:42:45 7 and it will be highlighted to identify whether it's the  
08:42:46 8 designation, the counterdesignation, or the rebuttal.

08:42:48 9 THE COURT: Thank you.

08:42:49 10 MR. SIPES: There's one evidentiary thing. The  
08:42:51 11 parties were mostly able to address and work out the  
08:42:53 12 evidentiary issues. I believe there's one remaining issue  
08:42:53 13 that my colleague Alaina Whitt will address.

08:42:57 14 Before we get there, Your Honor, I have a  
08:42:59 15 private matter to discuss with the Court. It's okay with me  
08:43:03 16 if counsel comes and addresses an issue that had come up from  
08:43:06 17 the court e-mail on Thursday that I was hoping to discuss with  
08:43:09 18 the Court in private off the record initially just to raise  
08:43:13 19 with the Court. It's not a big issue, but I would appreciate  
08:43:16 20 the opportunity.

08:43:18 21 THE COURT: I'm not sure I will -- I would allow  
08:43:21 22 sidebar, but it would be on the record.

08:43:24 23 MR. SIPES: It's actually a health issue which  
08:43:26 24 is why I wanted to just flag for you what it is, then you  
08:43:29 25 could decide what you want to put it on the record, if that

08:43:31 1 would be possible.

08:43:32 2 THE COURT: Well, I can seal that part. I'm  
08:43:34 3 just uncomfortable having discussions with counsel that's not  
08:43:38 4 on the record.

08:43:39 5 MR. SIPES: That would be fine. Thank you.

08:43:39 6 THE COURT: We'll have a sidebar and that  
08:43:41 7 portion of our discussion will be sealed.

08:43:43 8 Counsel, please approach.

08:43:45 9 MR. SIPES: I would appreciate it.

08:43:46 10 (Refer to a separate transcript for sealed 1)

08:46:28 11 MR. SIPES: With that, your Honor, I'll  
08:46:30 12 introduce my colleague Alaina Whitt who has the one remaining  
08:46:35 13 evidentiary issue.

08:46:36 14 THE COURT: Thank you.

08:46:41 15 MS. WHITT: Good morning. Alaina Whitt for  
08:46:44 16 plaintiffs.

08:46:44 17 We worked out -- as Chris mentioned, we worked  
08:46:45 18 out most of our evidentiary issues. We have one remaining.

08:46:49 19 On Saturday night defendants served an updated  
08:46:51 20 exhibit list adding about 30 exhibits after filing our  
08:46:55 21 complete exhibit list on Monday, pursuant to the Court's order  
08:46:59 22 regarding trial.

08:46:59 23 We -- we've objected to all but two of these  
08:47:02 24 exhibits as untimely. Two of them were created very recently.  
08:47:06 25 So we have -- we are fine with those being admitted. The



08:47:10 1 remaining --

08:47:10 2 THE COURT: Do I need to resolve this now?

08:47:13 3 In other words, so, I would rather proceed and  
08:47:16 4 set aside some time at the end of the day to resolve any  
08:47:21 5 disputes that you have about exhibits.

08:47:23 6 MS. WHITT: That's fine with us, Your Honor.

08:47:24 7 THE COURT: All right. I'll resolve it at the  
08:47:27 8 end of the day.

08:47:28 9 MS. WHITT: Okay.

08:47:29 10 THE COURT: Anything else before we proceed with  
08:47:32 11 openings?

08:47:32 12 MR. SIPES: No, Your Honor.

08:47:32 13 THE COURT: All right.

08:47:34 14 MR. SIPES: Good morning, Your Honor.

08:47:42 15 Christopher Sipes again on behalf of the Amarin plaintiffs.

08:47:44 16 I want to start this case with the patients who  
08:47:47 17 are at the center of the case. All of the patent claims at  
08:47:51 18 issue are claims for the treatment of patients with severe  
08:47:55 19 hypertriglyceridemia which I will try to remember to refer to  
08:47:55 20 as SHT or VHTG.

08:47:55 21 THE COURT: And if you are able to pronounce the  
08:47:55 22 full word, that's fine as well.

08:48:05 23 MR. SIPES: So the individuals whose  
08:48:09 24 triglyceride levels are very high is defined as more than  
08:48:12 25 500 milligrams per deciliter in the blood.

08:48:16 1 To give you some perspective, normal levels are  
08:48:18 2 below 150 milligrams per deciliter. So 500 and above is many  
08:48:25 3 times the normal level. In fact, their triglycerides  
08:48:29 4 sometimes can get so high that the blood begins to look milky  
08:48:31 5 or white.

08:48:31 6 These are patients who are very sick, but  
08:48:33 7 historically they have not been well-served by drug therapy.  
08:48:37 8 So let me start with why I say that they've been very sick.

08:48:41 9 First, they are at risk of cardiovascular  
08:48:45 10 disease. Elevated triglycerides are associated with an  
08:48:46 11 increased risk of cardiovascular events like heart attacks and  
08:48:50 12 strokes. In addition, many SHT patients have diabetes or  
08:48:56 13 metabolic disorder which further exacerbates the  
08:48:59 14 cardiovascular risk.

08:49:02 15 But even more seriously, they're at risk for  
08:49:05 16 pancreatitis which is a life threatening inflammation of the  
08:49:09 17 pancreas. Among other things, pancreatitis can lead to the  
08:49:13 18 leaking of digestive enzymes into the body cavity potentially  
08:49:15 19 leading to irrevocable organ damage and death.

08:49:20 20 So serious is the risk of pancreatitis that  
08:49:23 21 reduction of triglycerides takes precedence even over  
08:49:27 22 preventing heart attacks and strokes.

08:49:30 23 The first priority with patients with severe  
08:49:31 24 hypertriglyceridemia is to get their triglycerides down.  
08:49:33 25 Their secondary priority after that is to address their CV

08:49:39 1 risk.

08:49:39 2 So what causes SHT. SHT generally results from  
08:49:45 3 an underlying genetic disorder that drives up triglycerides  
08:49:47 4 and interferes with the body's ability to clear them.

08:49:50 5 Defendants in their pretrial briefing emphasize  
08:49:53 6 that TGs can become elevated from AN unhealthy lifestyle. Bad  
08:49:58 7 diet, excess alcohol consumption, lack of exercise, certain  
08:50:02 8 medications, can all contribute.

08:50:04 9 We believe it's rare here, even in that case, to  
08:50:07 10 get above 500 through lifestyle, and it's principally genetic.  
08:50:09 11 But this is a point of dispute between the parties, whether  
08:50:14 12 SHT is primarily a genetic disorder requiring chronic  
08:50:17 13 treatment or an acute lifestyle disorder that can be treated  
08:50:20 14 by diet and exercise alone.

08:50:22 15 For purposes of this case we can look to  
08:50:24 16 defendant's own drug labeling to tell us what kind of patients  
08:50:27 17 are at issue here.

08:50:28 18 And, Mr. Brooks, if we could pull up PX 1209.

08:50:32 19 This is one of the defendants' proposed  
08:50:34 20 labeling, Dr. Reddy's proposed labeling. And if we look at  
08:50:38 21 section 2.1, this is the section on dosage and administration,  
08:50:43 22 directions to doctors on what to do before initiating drug  
08:50:47 23 therapy with defendants' drugs. Identical labeling occurs in  
08:50:51 24 the other defendants' proposed labeling and in the Vascepa  
08:50:55 25 labeling.

08:50:55 1 If you look, for example, at the second bullet,  
08:50:57 2 it says,

08:50:58 3 "Patients should engage in appropriate  
08:50:59 4 nutritional intake and physical activity before  
08:51:01 5 receiving icosapent ethyl capsules."

08:51:05 6 The instruction in the labeling itself is to  
08:51:07 7 address those patients who can have their high triglycerides  
08:51:10 8 or very high triglycerides resolved through diet and  
08:51:14 9 exercise through diet and exercise. The drug is indicated for  
08:51:17 10 those patients who have the chronic form, who need drug  
08:51:20 11 therapy to break their triglycerides down.

08:51:24 12 You'll notice in the first bullet there is a  
08:51:25 13 similar discussion of trying to manage and address  
08:51:29 14 triglyceride elevations that occur through medications.

08:51:33 15 So the labeling itself is telling us that the  
08:51:35 16 patients at issue here are the patients with the chronic  
08:51:38 17 genetic form of the disease that will require long-going drug  
08:51:43 18 therapy to reduce and maintain their triglyceride levels.

08:51:47 19 This has confirmed as well by FDA's own review  
08:51:50 20 and approval of Vascepa NDA that led to the approved labeling  
08:51:55 21 at issue here.

08:51:56 22 And, Mr. Brooks, if we could pull up Plaintiff's  
08:52:00 23 Exhibit 289. This is the FDA's own Medical Review, the review  
08:52:04 24 of the clinical data underlying the labeling here. And I  
08:52:07 25 should point out this is a public document. Any interested

08:52:10 1 physician can get on FDA's website and review this document to  
08:52:15 2 understand the scope of the labeling.

08:52:18 3 If we could turn to page 00011, Mr. Brooks, we  
08:52:21 4 pull up -- FDA itself says what kind of patients we were  
08:52:25 5 talking about. It says,

08:52:26 6 "Very high triglycerides, greater than or  
08:52:28 7 equal to 500 milligrams per deciliter, has a strong  
08:52:31 8 genetic component and is associated with an  
08:52:34 9 increasing risk for acute pancreatitis. The most  
08:52:37 10 frequently reported...defects for persons with very  
08:52:41 11 high triglycerides are...."

08:52:42 12 And it goes on to describe the genetic defects  
08:52:45 13 that found in these patients.

08:52:47 14 I won't belabor them but I will note, because  
08:52:50 15 we'll come back to it, the most common defects interfere with  
08:52:52 16 the action of an enzyme in the body called lipoprotein lipase  
08:52:52 17 which you will hear is an enzyme that helps the body clear  
08:52:52 18 triglycerides which are carried in particles called VLDL  
08:53:03 19 particles, but we'll come back to that.

08:53:05 20 Let me look as well at page 000142 of the  
08:53:07 21 Medical Review, and, Mr. Brooks, if you could highlight  
08:53:10 22 questions 21 and 22. This is a very simple checklist that the  
08:53:14 23 FDA has to ensure that the proper evidence has been introduced  
08:53:18 24 as part of the clinical package for approval of the  
08:53:21 25 indications sought.

08:53:23 1 And you'll see, for example, question 21,  
08:53:25 2 "For chronically administered drugs, have an  
08:53:28 3 adequate number of patients (based on ICH guidelines  
08:53:33 4 for exposure) been exposed at the dose (or dose  
08:53:36 5 range) believed to efficacious?"

08:53:38 6 And it's checked yes. So, in fact, Amarin did  
08:53:41 7 submit sufficient data for a chronically administered drug  
08:53:41 8 here.

08:53:45 9 The next question,  
08:53:45 10 "For drugs not chronically administered  
08:53:48 11 (intermittent or short course), have the requisite  
08:53:51 12 number of patients been exposed as requested by the  
08:53:54 13 Division?"

08:53:55 14 And it's checked not applicable. This is not an  
08:53:57 15 acute or intermittent or short course indication. This is a  
08:54:01 16 chronically administered indication, and that's clear from  
08:54:05 17 FDA's own public Medical Review.

08:54:08 18 Now, let me go back to why did I say that these  
08:54:09 19 were patients that were historically poorly served.

08:54:14 20 Very few drugs are power enough at lowering  
08:54:18 21 triglycerides to be approved as a treatment for SHT. Until  
08:54:22 22 Vascepa, every single one of them reduced triglycerides in  
08:54:26 23 severely hypertriglyceridemic patients only at the expense of  
08:54:31 24 dramatically raising LDL-C, the bad cholesterol, the  
08:54:31 25 cholesterol that exacerbates cardiovascular risk.

08:54:37 1 That is, until Vascepa, SHT patients could only  
08:54:41 2 treat their very high triglycerides at the expense of  
08:54:45 3 exacerbating their risk of CV events. This was a concern that  
08:54:48 4 was expressed in the literature very long ago.

08:54:52 5 Mr. Brooks, if we could pull up PX 1026.

08:54:54 6 This is an article by Carlson in *The Journal of*  
08:54:58 7 *Atherosclerosis* from 1977, and it is reporting on a study of  
08:55:03 8 niacin to treat very high triglycerides.

08:55:05 9 And, Mr. Brooks, if we go to page 0007, if you  
08:55:09 10 can blow up the middle paragraph.

08:55:11 11 The article that was the clinical study reported  
08:55:15 12 that LDL-C cholesterol went up very high, and the authors  
08:55:22 13 observed the finding of, emphasized.

08:55:23 14 "...major clinical concern in this report is  
08:55:26 15 the sometimes quite substantial rise in LDL  
08:55:30 16 cholesterol. This may be quite atherogenic and  
08:55:35 17 theoretically the benefit of lowering the VLDL,"  
08:55:38 18 that's the lipoprotein that carries TGs "in these  
08:55:42 19 patients may be overridden by the potential danger  
08:55:48 20 due to the rise in LDL."

08:55:48 21 So this was concern expressed all the way back  
08:55:50 22 in 1977. Since then fibrates like Fenofibrate and Lovaza and  
08:55:58 23 omega-3 mixture product have been approved, but all of them  
08:56:00 24 raise LDL-C in SHT patients by around 45 to 50 percent.

08:56:06 25 To put that in perspective, a patient who came

08:56:08 1 in with an LDL of a hundred, would end up with an LDL of  
08:56:12 2 around 150. That's a serious increase in their CV risk, but  
08:56:16 3 that was the price the patients had to pay in order to address  
08:56:20 4 their very high triglycerides and avoid pancreatitis, and it  
08:56:24 5 was a necessary price because of the seriousness of  
08:56:25 6 pancreatitis.

08:56:25 7 There were other problems with some of these  
08:56:28 8 treatments. Niacin has terrible side effects. Fibrates have  
08:56:32 9 interaction problems with statins. But the most serious  
08:56:34 10 concern was this dramatic rise in LDL-C.

08:56:38 11 So universal was the increase in LDL-C  
08:56:43 12 accompanying the reduction in triglycerides in SHT patients  
08:56:47 13 that it was believed to be a necessary consequence of the TG  
08:56:50 14 reduction itself rather than simply a side effect of the  
08:56:54 15 particular agent used.

08:56:55 16 I think to understand why it is helpful to go  
08:56:58 17 through how TGs are carried in the blood, and we've prepared a  
08:57:02 18 slide, Mr. Brooks, if you could pull that up.

08:57:04 19 This is simple diagram of the carrying of  
08:57:07 20 triglycerides in the blood. They are made in the liver, and  
08:57:11 21 they are put into a lipoprotein which is called VLDL, very  
08:57:15 22 low-density lipoprotein, and it contains both triglycerides  
08:57:19 23 and cholesterol.

08:57:21 24 The triglycerides are shown in red, the  
08:57:24 25 cholesterol in yellow.



08:57:27 1 And these are -- these particles pass through  
08:57:27 2 the bloodstream. The triglycerides serve as fuel for cells,  
08:57:31 3 and the cholesterol is used as a precursor for things like  
08:57:35 4 hormones so they're delivered to cells in the body.

08:57:37 5 As these VLDL particles pass through the  
08:57:42 6 bloodstream, an enzyme, lipoprotein lipase, helps to pick off  
08:57:43 7 the triglycerides, and ultimately what happens is the VLDL,  
08:57:47 8 these large VLDL particles, shrink down as the triglycerides  
08:57:51 9 are removed becoming first IDL, intermediate density  
08:57:51 10 lipoproteins, and then ultimately LDL, low-density  
08:57:51 11 lipoproteins.

08:58:00 12 So you can see that the VLDL particles are  
08:58:02 13 cleared through removal of triglycerides to become LDL.

08:58:06 14 What happens with very high triglyceride  
08:58:10 15 patients is they're stuck. They have trouble clearing the  
08:58:13 16 VLDL, so they get a huge excess of the LDL. They make too  
08:58:17 17 much. And then because their lipoprotein lipase enzyme is  
08:58:20 18 impaired, they can't clear them. And so they have a big  
08:58:24 19 superabundance of VLDL. That's why they have so much  
08:58:27 20 triglycerides.

08:58:28 21 When medication is given -- excuse me. When  
08:58:30 22 they get medication, that helps to clear the VLDL. It's like  
08:58:35 23 uncorking the bottle. All that VLDL is cleared into LDL.

08:58:39 24 So it was quite natural to believe that in  
08:58:41 25 treating very high triglycerides with medication, all this

08:58:45 1 excess VLDL would clear to LDL and the LDL would go way up.

08:58:50 2 And, in fact, this reasoning continued through into 2008, for  
08:58:54 3 example, the McKenney 2007 paper.

08:58:58 4 If we could, Mr. Brooks, pull PX 923.

08:59:03 5 So this is a publication from 2007 describing a  
08:59:06 6 then relatively new omega-3 product Lovaza which had been  
08:59:12 7 approved to treat very high triglycerides, and it showed about  
08:59:17 8 a 50 percent rise in LDL-C.

08:59:20 9 Mr. Brooks, if we go to page 005 and blow up the  
08:59:23 10 bottom right-hand corner.

08:59:26 11 In discussing the pharmacokinetics, the way the  
08:59:29 12 product works, the authors observe,

08:59:32 13 "Importantly, the conversion of VLDL to LDL  
08:59:35 14 particles increased 93 percent under the influence of  
08:59:39 15 prescription omega-3 fatty acids. These results  
08:59:43 16 illustrates that the enhanced catabolism of  
08:59:46 17 triglycerides produced by prescription omega-3 fatty  
08:59:48 18 acids results in less secretion and more rapid  
08:59:51 19 removal of VLDL particles. The results also show  
08:59:55 20 that VLDL particles are" thus "rapidly converted to  
09:00:00 21 LDL particles, thus explaining why LDL cholesterol  
09:00:03 22 levels may rise in patients with very high  
09:00:06 23 triglycerides when given prescription omega-3 fatty  
09:00:06 24 acid therapy."

09:00:10 25 So there was, in essence, a belief that it was

inevitable, that the necessary consequence of treating severely hypertriglyceridemic patients to clear their triglycerides would raise their LDL-C in patients.

In fact, before initiating the trial that demonstrated the effectiveness of EPA in treating very high triglycerides, the so-called MARINE trial, Amarin convened an expert panel, a panel of outside experts to give them advice on the meeting.

And, Mr. Brooks, if we pull up PX 754.

This was the meeting of December of 2008 in Boston. It was a confidential meeting that Amarin convened to advise them on this trial, the MARINE trial.

If we go to the second page, Mr. Brooks.

You'll see these are the main comments from experts, and one of their comments is LDL-C --

"LDL-C is likely to go up as it does in virtually all TG-lowering therapies in this group of patients."

There was just a belief among not just people of ordinary skill, but really even people of extraordinary skill, that LDL-C just had to go up when you reduce triglycerides in very high triglyceride patients.

It turns out that's not true of EPA. Now, we don't exactly know why purified EPA doesn't cause this. It may well be the very same mechanism does result in an increase

09:01:35 1 in LDL-C, but EPA has other effects to reduce LDL-C, and we  
09:01:41 2 don't really know why.

09:01:42 3 But it turns out that after the MARINE trial  
09:01:44 4 that Vascepa became the first and only treatment for severe  
09:01:49 5 hypertriglyceridemia that was actually able to reduce  
09:01:52 6 triglycerides in these patients without raising the LDL-C.

09:01:56 7 This point was conceded by defendants' own  
09:01:58 8 retained expert, Dr. Heinecke, and we have his testimony here  
09:02:02 9 where he acknowledges that among a long string of products  
09:02:05 10 that have been approved for treatment of this condition,  
09:02:08 11 Vascepa stands alone as the only one that was able to reduce  
09:02:12 12 triglycerides without increasing LDL-C.

09:02:15 13 So, Mr. Brooks, if we can play that.

09:02:29 14 (Video recording played.)

09:03:02 15 So, Your Honor, not surprisingly, this was a  
09:03:31 16 rather dramatic result. But it's not just about numbers  
09:03:34 17 because Amarin has gone on and shown that not only is Vascepa  
09:03:39 18 able to reduce triglycerides without raising LDL-C but it  
09:03:46 19 actually reduces cardiovascular risk, and it reduces  
09:03:52 20 cardiovascular risk actually on top of a statin, and it's the  
09:03:52 21 first approved treatment for that as well.

09:03:54 22 So if we look at PX 1185 at 01, this is FDA's  
09:03:59 23 press release from December 13th of last year after the  
09:04:02 24 REDUCE-IT trial.

09:04:04 25 FDA noted,

09:04:06 1 "Vascepa is the first FDA approved drug to  
09:04:09 2 reduce cardiovascular risks among patients with  
09:04:14 3 elevated triglyceride levels as an add-on for  
09:04:14 4 maximally tolerated statin therapy."

09:04:14 5 Vascepa is thus the first approved treatment for  
09:04:23 6 severe hypertriglyceridemia shown to provide a cardiovascular  
09:04:26 7 benefit to those patients in addition to reducing their TGs.  
09:04:30 8 So this is a dramatic step forward for treatment of patients  
09:04:34 9 with severe hypertriglyceridemia.

09:04:37 10 Not surprisingly, Vascepa has received industry  
09:04:43 11 wide praise and recognition for this. As soon as the first  
09:04:43 12 trial, the MARINE trial, results were announced people  
09:04:46 13 recognized their significance.

09:04:48 14 If we could pull up PX 929, Mr. Brooks.

09:04:53 15 This is a press report from 2010 on release of  
09:04:57 16 the MARINE trial results. And on the second page, Mr. Brooks,  
09:05:00 17 there's quotation from Mr. Steven Nissen, of the Cleveland  
09:05:05 18 clinic who is quite knowledgeable on cardiovascular matters.  
09:05:09 19 He says,

09:05:10 20 "This is real advance in the treatment of  
09:05:14 21 elevated triglycerides."

09:05:16 22 "It gives you all of the benefits without  
09:05:17 23 the downside."

09:05:18 24 He goes on to say, "There's still room for  
09:05:20 25 small companies to do innovative things...."

09:05:23 1 Similarly, PX 959, this is the editorial from  
09:05:29 2 *The New England Journal of Medicine* after the release of the  
09:05:33 3 REDUCE-IT trial which showed cardiovascular improvements.

09:05:34 4 And, again, Mr. Brooks, if we could pull up,  
09:05:39 5 thank you, the bottom paragraph there.

09:05:40 6 The editorial goes on to say,

09:05:41 7 "We welcome these results with surprise,  
09:05:45 8 speculation, and hope. Most surprising was the  
09:05:48 9 difference between the results of REDUCE-IT and those  
09:05:50 10 of many previous trials of n-3 fatty acids," which  
09:05:55 11 are omega-3 fatty acids.

09:05:59 12 So Amarin through Vascepa has had a real world  
09:06:02 13 impact on the treatment of patients at risk. In 2019 alone,  
09:06:04 14 even before FDA approved the new labeling, the American  
09:06:08 15 Diabetes Association, the American Heart Association, the  
09:06:12 16 National Lipid Association, the European Society of  
09:06:19 17 Cardiology, and the European Atherosclerosis Society, all had  
09:06:19 18 charged their treatment guidelines directing them to use of 4  
09:06:23 19 grams per day of purified EPA to address cardiovascular risk  
09:06:26 20 in patients with elevated triglycerides.

09:06:29 21 So Amarin has changed the practice of medicine  
09:06:32 22 because of these trials. So who is Amarin?

09:06:35 23 Amarin is a single product company. It has  
09:06:37 24 devoted its history and resources to the development of EPA  
09:06:42 25 and Vascepa.

09:06:42 1 Its conducted a number of clinical trials  
09:06:45 2 through its predecessor Laxdale. It conducted a number of  
09:06:45 3 trials in CNS, neurological indications, Huntington's disease,  
09:06:53 4 schizophrenia, and depression.

09:06:54 5 These failed to meet their end points to support  
09:06:56 6 their indications as many clinical trials do, but it provided  
09:07:00 7 Amarin scientists with extensive and unique information on  
09:07:07 8 EPA's actions in the body, and that's what then led to these  
09:07:07 9 cardiovascular indications.

09:07:09 10 The first was the MARINE trial we talked about  
09:07:12 11 showing its effects in severe hypertriglyceridemia. It then  
09:07:15 12 did two subsequent cardiovascular trials, ANCHOR and  
09:07:18 13 REDUCE-IT, that were addressed to show the cardiovascular  
09:07:22 14 benefit, and that is where we are today.

09:07:23 15 Who are the inventors? You will get deposition  
09:07:26 16 testimony from two of Amarin inventors, Mehar Manku. He is a  
09:07:32 17 lipidologist. He has decades of experience with omega-3 fatty  
09:07:36 18 acids and extraordinary knowledge of EPA both from the  
09:07:39 19 literature and from those proprietary clinical trials from  
09:07:42 20 Amarin and Laxdale. This gave him insights into the  
09:07:44 21 biological of EPA that no one else had.

09:07:47 22 Another is Ian Osterloh. He's a clinician with  
09:07:52 23 expertise in CV drug clinical development. In fact, he was  
09:07:55 24 one of the inventors of the Viagra methods of use. So he has  
09:07:58 25 already shown the ability to perceive unexpected effects of

09:08:02 1 drugs.

09:08:03 2 Both are older and retired and living in the  
09:08:06 3 north and east of England. Unfortunately, neither will be  
09:08:10 4 here live, but you will receive extensive testimony in  
09:08:12 5 deposition form from them.

09:08:12 6 In terms of infringement, we recognize that the  
09:08:12 7 Court has had extensive briefing already on the infringement  
09:08:19 8 issues so I won't belabor those points this morning. I should  
09:08:22 9 note that based on the defendants' pretrial brief, I think  
09:08:25 10 there's a dispute about the basic issue about how the Court  
09:08:28 11 should assess inducements.

09:08:30 12 In their pretrial brief on pages 13 to 14,  
09:08:32 13 defendants assert that the existence of a substantial  
09:08:37 14 noninfringing use negates an inducement to infringe. In  
09:08:39 15 essence, they're saying that as long as some physicians are  
09:08:42 16 led not to carry on, to carry a noninfringing method, there's  
09:08:46 17 no inducement. That's wrong.

09:08:48 18 In fact, the Federal Circuit recently has  
09:08:50 19 rejected the defendants' exact argument, in fact, West-Ward's  
09:08:55 20 own arguments, in a case called *Vanda Pharmaceuticals v*  
09:08:59 21 *West-Ward*.

09:09:00 22 They cite *Warner-Lambert*, a 2003 case, but in  
09:09:00 23 *West-Ward*, 887 F.3d 1117 at 1132 to 33, they note that  
09:09:00 24 West-Ward's reliance on Warner-Lambert, an off-label use case,  
09:09:16 25 is misplaced, and goes on to point out that substantial



noninfringing use is not a defense to induced infringement.

The proper standard, and they quote the AstraZeneca and Eli-Lilly cases is,

"Evidence that the product labeling that defendants seek would inevitably lead some physicians to infringe establishes the requisite intent for inducement."

Under this proper analysis, Your Honor, we believe infringement here is clear because each defendants' proposed labeling will inevitably lead some physicians to treat some patients in accordance with the claims' methods of treatment. So we think inducement here is very clear.

Let me talk briefly been obviousness. Their only invalidity defense is obviousness. Defendants are not asserting anticipation in the prior art, that is, they have conceded that the claim methods of treating severe hypertriglyceridemia with purified EPA are novel. The only question is whether the prior art renders then obvious.

To prevail on their defense, defendants must show with clear and convincing evidence that the prior art itself would have motivated a person of ordinary skill in the art to carry out the claim methods of treating severe hypertriglyceridemia and a reasonable expectation of success in achieving the claimed results.

None of defendants' actual cited prior art

09:10:29 1 suggest a benefit of purified EPA in patients with severe  
09:10:34 2 hypertriglyceridemia, and this a fatal flaw in defendants'  
09:10:36 3 case.

09:10:37 4 We believe that the evidence will show that this  
09:10:39 5 is a distinct patient population whose therapeutic needs and  
09:10:43 6 treatment response were understood to be distinct and  
09:10:46 7 different from others.

09:10:47 8 There was no prior art that provided motivation  
09:10:50 9 to use purified EPA to treat severe hypertriglyceridemia, and  
09:10:53 10 no reasonable expectation that doing so would provide clinical  
09:10:57 11 benefits such as avoiding the rise in LDL-C that had been seen  
09:11:02 12 in every prior treatment.

09:11:03 13 Defendants' rely heavily, for example, two prior  
09:11:10 14 art studies, Mori 2000 and Hayashi 1995. Mori 2000 was  
09:11:10 15 actually studying an entirely different patient population in  
09:11:18 16 one with just slightly elevated TGs, and there it actually  
09:11:18 17 reported a three-and-a-half percent elevation in LDL-C, and,  
09:11:21 18 of course, there are even agents that reduce LDL-C in those  
09:11:26 19 patients, but show a dramatic rise in LDL-C in SHT patients.

09:11:30 20 For example, Fenofibrate will reduce LDL-C in  
09:11:35 21 the very patients studied in Mori but show almost a 50 percent  
09:11:36 22 increase in LDL-C in SHT patients. SHT patients just respond  
09:11:42 23 differently, and it was recognized in the art they were prone  
09:11:46 24 to very high increases in LDL-C.

09:11:48 25 The other paper that they cite to is Hayashi

1995. Hayashi 2 was really focused on patients with lower triglycerides. Defendants assert that there were some patients who happened to be in the Hayashi study. There's some dispute over that, but one thing is clear, there's no reported data for those patients over 500 milligrams per deciliter, and, indeed, the method that Hayashi used to determine LDL-C doesn't even work in those patients so that paper has no bearing on the treatment of severe hypertriglyceridemia.

So the actual prior art they rely on doesn't render the claimed methods here obvious. Instead, defendants try to refocus it by focusing on Amarin's own statements, and they cite extensively from Amarin's internal documents and Amarin's confidential presentations or submissions to FDA.

That is not the right path to making out an obviousness case. Obviously Amarin, and the inventors had unique insights into therapeutic effects of EPA and took advantage of them.

If the inventors' own path were a way of showing obviousness, there would be no valid patents. Inventors have unique insights, and it is improper to rely upon Amarin's own documents to prove obviousness.

So what is at stake in this case?

Amarin has invested the last ten years to developing the Vascepa product and demonstrating to FDA and

the medical community that it has significant real world clinical benefits for patients with elevated triglycerides, including those with severe hypertriglyceridemia.

There can be no dispute that Amarin has succeeded in that quest. As FDA observed in approving a new indication, Vascepa is the first drug approved to reduce CV risk in patients with elevated TGs as an add-on to statins.

Vascepa has the potential to save tens of thousands of lives, including many patients with severe hypertriglyceridemia, and Amarin achieved this at considerable risk.

Defendants' own retained expert, Dr. Heinecke, whose testimony we saw earlier, was quoted as saying in 2008 that if FDA was going to require cardiovascular outcome trials, we are not going to have many new approved drugs. He recognized at the time the expense, the risk, and the uncertainty of trying to prove cardiovascular benefit.

But Amarin took that risk and it succeeded. As Dr. Steven Nissen observed after the MARINE trial, Amarin's story shows that there's still room for small companies to do innovative things. The question that this case will answer is whether Amarin is to enjoy the fruits of its success.

Defendants make much in their pretrial brief of the fact that they have, quote, carved out of their proposed labeling the new cardiovascular indication. To be clear, this

09:14:34 1 case should and must be decided on the basis of the labeling  
09:14:37 2 they are seeking, but understand that defendants, if approved,  
09:14:41 3 are seeking to be deemed interchangeable and likely will be  
09:14:45 4 deemed interchangeable with Vascepa, and that means regardless  
09:14:48 5 of the carved-out labeling, their product will be substituted  
09:14:52 6 at the pharmacy for all prescriptions including REDUCE-IT  
09:14:57 7 prescriptions.

09:14:58 8 So that doesn't change the legal analysis here,  
09:15:00 9 but it does mean Amarin's future depends on this case.

09:15:04 10 So defendants are wrong in saying that this case  
09:15:06 11 is simply about Amarin's desire to block generics. This case  
09:15:11 12 is about the industry's incentive to innovate and whether the  
09:15:15 13 time spent in conducting cardiovascular outcome trials, trials  
09:15:19 14 which are long and expensive, will earn a reward.

09:15:23 15 That question, I think, is why so many people  
09:15:25 16 are watching this case. This case is equally about whether  
09:15:27 17 the Hatch-Waxman system provides adequate protection to  
09:15:31 18 preserve the incentive to innovate, particularly in situations  
09:15:35 19 like this when a clinical program requires years to complete.

09:15:39 20 We believe the evidence here will show that  
09:15:41 21 Amarin's patent claims are both infringed, and that defendants  
09:15:44 22 have not met their burden to prove obviousness.

09:15:47 23 Thank you, Your Honor.

09:15:48 24 THE COURT: Thank you, Mr. Sipes.

09:15:49 25 And I should have mentioned earlier that I have

09:15:50 1 reviewed the parties' trial briefs, the plaintiffs' trial  
09:15:53 2 brief as well as the defendants' sealed trial brief.

09:15:56 3 And I think the issues are thoroughly briefed,  
09:15:59 4 and I know that while the parties appeal to all these public  
09:16:02 5 policies, ultimately the issues are rather straightforward in  
09:16:06 6 terms of induced infringement and obviousness, but thank you.

09:16:09 7 Let me hear from defense counsel.

09:16:16 8 MR. KLEIN: Thank you, Your Honor.

09:16:18 9 We do have some slides, and while they're being  
09:16:21 10 put up, I just want to bring the Court's attention to a  
09:16:24 11 Federal Circuit case *United States* -- I'm sorry, *AstraZeneca v*  
09:16:31 12 *Apotex* from 2012, and the cite 669 F.3d 1370, and it gets to  
09:16:35 13 the very point Your Honor made which is that the market  
09:16:38 14 realities of automatic substitution are absolutely irrelevant  
09:16:42 15 to this case, and that is -- that's established law.

09:16:46 16 Before I dive into the slides and the specific  
09:16:49 17 issues of noninfringement and obviousness, I'd like to start  
09:16:53 18 with an overview of the case.

09:16:56 19 As Your Honor pointed out, this case is  
09:16:59 20 straightforward. It's about fish oil. Fish oil has been  
09:17:03 21 available as supplements and as pharmaceutical products for a  
09:17:09 22 long time.

09:17:10 23 There are five listed inventors on the  
09:17:13 24 patents-in-suit. Not one of them is coming into this court to  
09:17:17 25 explain what they purportedly invented.

09:17:20 1 Normally in these cases the inventor comes in,  
09:17:22 2 maybe opens up a lab notebook, talks about what was done  
09:17:25 3 before the patent application, what was discovered, what was  
09:17:29 4 novel that supports the very rich reward of patent  
09:17:33 5 exclusivity. That's not this case.

09:17:36 6 The only time you're going to hear from the  
09:17:38 7 inventors is in the designated testimony. And Your Honor may  
09:17:42 8 have the same impression that we had from the designated  
09:17:45 9 testimony. It's unclear what many of these inventors even  
09:17:48 10 did, and, at most, all they did was help develop this Vascepa  
09:17:56 11 product based on the prior art.

09:17:58 12 There is no invention story here because there  
09:18:02 13 is no invention, and so Amarin is trying to change the topic.  
09:18:08 14 Instead of focusing on what Amarin did before filing its  
09:18:12 15 patent application, Amarin is focusing on clinical trials that  
09:18:16 16 were conducted well after the application was filed. And, to  
09:18:20 17 be clear, the evidence will show that these clinical trials  
09:18:24 18 were confirmatory clinical trials. They confirmed what was  
09:18:28 19 either known in the prior art or what was reasonably expected.

09:18:32 20 And the reward for conducting a successful  
09:18:38 21 confirmatory clinical trial that results in FDA approved  
09:18:42 22 indications, which is what they got, it's not patent  
09:18:45 23 exclusivity, it's regulatory exclusivity, and Amarin has  
09:18:50 24 already received seven-and-one-half years of regulatory  
09:18:55 25 exclusivity because of its MARINE clinical trial in the first

09:19:01 1 indication, and that period of exclusivity is about to expire  
09:19:04 2 at the end of this month. And the evidence will show that  
09:19:06 3 Amarin is not entitled to rely on its patents to further block  
09:19:12 4 generic competition, much less for ten years.

09:19:15 5 Now, with that, Your Honor, I would like to  
09:19:18 6 start turning to the slides, and we created a simple timeline  
09:19:22 7 that hopefully will orient the Court with regard to some key  
09:19:27 8 events and key documents.

09:19:28 9 And I want to start all the way back in 1991.  
09:19:33 10 This is when the Japanese authorities approved a purified EPA  
09:19:39 11 product called Epadel, and Epadel was indicated, among other  
09:19:46 12 things, to reduce triglycerides.

09:19:49 13 By 2007, which is before the claimed and  
09:19:52 14 disputed conception date of March 2008, Epadel was 98 percent  
09:19:58 15 pure. So you're not going to hear Amarin come in this --  
09:20:01 16 come -- make the claim that it invented purified EPA or that  
09:20:05 17 it discovered it reduces triglycerides. That was long known.

09:20:11 18 In 2004, the FDA approved a product with the two  
09:20:15 19 components of fish oil, EPA and DHA, for the exact method of  
09:20:21 20 treatment covered by the claims, treating very high  
09:20:24 21 triglycerides.

09:20:24 22 There's a side effect in the label, and I'll  
09:20:28 23 talk about that in the -- a bit later. In some patients,  
09:20:33 24 LDL-C increases, and I'll get back to that in a moment.

09:20:37 25 In 2007 -- and you didn't hear anything about



09:20:42 1 this from counsel. In 2007, a very significant clinical study  
09:20:48 2 was published in what is one of the most prestigious  
09:20:54 3 scientific publications on the planet, *The Lancet*, and this  
09:20:59 4 publication wasn't some small study, it involved 18,000  
09:21:04 5 Japanese patients and lasted about four-and-a-half years.

09:21:07 6 And this reference, referred to as Yokoyama,  
09:21:15 7 reached a conclusion that is unambiguous. EPA is a promising  
09:21:16 8 treatment for prevention of major coronary events. Amarin  
09:21:21 9 would like you to believe that they discovered this, but they  
09:21:24 10 certainly did not. This was reported in the literature back  
09:21:27 11 in 2007.

09:21:31 12 In March 2008, Amarin's documents indicate that  
09:21:35 13 it's starting to prepare a submission to the FDA with regard  
09:21:37 14 to Vascepa. The code name is AMR 101.

09:21:42 15 Now, just stepping back a moment, you heard from  
09:21:45 16 counsel that before this Amarin was trying to develop EPA for  
09:21:50 17 something totally different, Huntington's disease,  
09:21:55 18 schizophrenia, depression, and those trials failed, and when  
09:21:58 19 those trials failed, Amarin had this purified EPA and looking  
09:22:02 20 for other options, and what Amarin decided to do was develop  
09:22:06 21 the prior art EPA for the Lovaza indication.

09:22:09 22 In essence, Amarin took Epadel, or an  
09:22:13 23 Epadel-like product, Epadel is a lower dose, to the United  
09:22:16 24 States and sought approval for an indication that had already  
09:22:20 25 been approved for a similar product.

09:22:22 1           Amarin says in its internal documents that it  
09:22:25 2 expects that an outcome study will not be required given the  
09:22:30 3 clinical evidence already available to date. Amarin is  
09:22:34 4 relying on the prior art.

09:22:35 5           This same document identifies not only Epadel  
09:22:38 6 and JELIS, but also the Mori reference. The Mori reference  
09:22:44 7 used four grams of purified EPA. That is the dose in the  
09:22:49 8 claims.

09:22:50 9           And Mori concluded that the LDL-C, this bad  
09:22:54 10 cholesterol, increased significantly with DHA but not with  
09:22:58 11 EPA. Counsel said that there was 3.5 increase in EPA, but  
09:23:03 12 that was found not to be statistically significant. It's  
09:23:06 13 essentially no increase.

09:23:07 14           And Amarin itself relied on this prior art.  
09:23:11 15 This -- this reference is not linked to the inventors as far  
09:23:15 16 as I can tell, and it's before the alleged date of conception.

09:23:19 17           About a year later, in February 2009, Amarin  
09:23:24 18 files its patent application. At this point, Your Honor,  
09:23:27 19 Amarin had not used purified EPA in a single patient with very  
09:23:32 20 high triglycerides. Amarin relied solely on the prior art to  
09:23:36 21 file this patent application.

09:23:38 22           A year later, Amarin is trying to entice  
09:23:43 23 investors to invest in the company for the development of  
09:23:46 24 Vascepa, and to convince the investors that the Vascepa is a  
09:23:51 25 promising product, Amarin tells the investors that the prior

art had already demonstrated that EPA is LDL neutral.

This is what Amarin claims to have invented?

In March 2010, Amarin is telling the investors that they didn't invent it. This is discussed in six prior art references, none of them were authored by Amarin, and these include the Mori reference we rely on, as well as the Kurabayashi reference.

It's not until November 2010 that Amarin gets the results from the MARINE study, and, as expected, in view of Mori and those other reference, the median LDL-C did not increase. So, in essence, the median data was LDL neutral, what Amarin was telling investors.

So Amarin prepares a manuscript, wants to publish the results of the clinical trial data, and, of course, Amarin has this -- their patent applications pending, and so they prepare a manuscript and say that Vascepa did not increase LDL-C levels, and this was an unexpected finding. That's what they put in their manuscript. And you can see unexpected is actually a little smudged, and that's because it's highlighted in the original.

And they send this manuscript to Dr. Bays who was the principal MARINE investigator, and Dr. Bays is not an inventor, he's looking at this from a scientific perspective, not from a patent perspective.

And he writes this e-mail, and he says the

statement below that this finding that -- that Vascepa did not increase LDL levels was unexpected is in contradiction to the rest of the manuscript. The manuscript cites the Mori reference.

"My initial sense is that it largely guts the current storyline of the paper and the reality of this drug development program."

The drug development program, the reality is that Amarin developed Vascepa based on the prior art. That is the reality.

So this gets us to REDUCE-IT. We expect you're going to hear an awful lot about the REDUCE-IT study, but, Your Honor, this is a side show. REDUCE-IT is not relevant to this case, and I'll get to that in more depth later.

But, most importantly, the results of REDUCE-IT were expected. They confirmed the results of the JELIS trial. And today, and in this trial, Amarin, I believe, is going to try to trash the results of the JELIS trial saying that there were methodological flaws or was unreliable.

But at the time that's not what they said internally. It's not what they told investors, and it's not what they told the FDA.

This is letter from 2014 to the FDA from Amarin characterizing JELIS as a very large, well-designed study, and Amarin believes that its results should not be dismissed

1 lightly. Again, JELIS found cardiovascular benefits from  
2 purified EPA. REDUCE-IT confirmed that.

3 Turning now to the issues, the two issues  
4 starting with noninfringement, and I want to get to the heart  
5 of Your Honor's summary judgment ruling and start with that,  
6 but I do want to make a couple points in response to counsel's  
7 arguments.

8 Number one, the inquiry is absolutely limited to  
9 our label. It doesn't include the Lovaza label. It doesn't  
10 include the FDA medical forms that you saw in openings. That  
11 is clear.

12 Number two, with regard to the relevance of  
13 substantial noninfringing use, counsel mischaracterized our  
14 argument. The law is clear, and this is in the *Horizon* case.  
15 If there's a substantial noninfringing use, you cannot imply  
16 inducement. You cannot imply specific intent. There can  
17 still be induced infringement, but you have to point to some  
18 language, some instruction in the label, and this gets to Your  
19 Honor's ruling.

20 Amarin has a very narrow window to prove induced  
21 infringement in this case because the label does not  
22 explicitly instruct doctors to use icosapent for at least  
23 12 weeks.

24 The only way they can prove inducement under the  
25 case law is by showing that the term severe

hypertriglyceridemia necessarily means to physicians that they have to give the drug for at least 12 weeks, and the theory, as we understand it, is that, if doctors read the label, know for a fact for every patient they have to give the drug for 12 weeks, well, then, maybe the label doesn't have to explicitly say that.

But unless doctors know severe hypertriglyceridemia is a chronic condition requiring definite treatment and requiring 12-week drug therapy, they cannot meet their burden, and they will not. The evidence will show they will not meet their burden.

Your Honor wanted to hear from the clinicians so I have a few deposition quotes to give Your Honor a taste of what you can expect to hear at trial.

This is Dr. Budoff, Amarin's primary infringement expert, and he concedes that roughly one fifth of patients with severe hypertriglyceridemia are able to reduce their triglyceride levels below 500 through diet and exercise alone. This is a critical concession. Twenty percent of patients. And the number -- he -- Dr. Budoff is a specialist. The number is probably higher in the general severe hypertriglyceridemia public.

He concedes that 20 percent of patients don't even need any drug therapy. Doctors know this. When they see the term severe hypertriglyceridemia, they know that some

09:29:53 1 patients have some -- a genetic issue, it's a very small  
09:29:59 2 minority, they may need long term drug therapy, but at least  
09:30:02 3 20 percent don't need any drug therapy, and all of these  
09:30:05 4 patients could benefit from a short term course of icosapent  
09:30:10 5 that drops the triglycerides immediately, eliminates the risk  
09:30:14 6 of pancreatitis, and then the patients don't have to bother  
09:30:17 7 taking four pills twice a day because they can maintain levels  
09:30:22 8 below 500 with diet and exercise alone.

09:30:25 9 Dr. Toth is Amarin's validity expert. He  
09:30:29 10 concedes that there could be circumstances where severe  
09:30:33 11 hypertriglyceridemia is an acute phenomenon. This is the  
09:30:37 12 opposite of what they need to prove.

09:30:38 13 And a classic example, Your Honor, is some  
09:30:42 14 patients have a genetic predisposition to a triglyceride level  
09:30:46 15 of around 400, not severe, but very high. Those patients can  
09:30:51 16 experience spikes above 500, for example, if they drink too  
09:30:55 17 much alcohol, if they're smoking, if they take medications  
09:30:59 18 like estrogen or corticosteroid.

09:31:02 19 Their triglycerides can spike above 500, but  
09:31:05 20 it's temporary. If they stop drinking the alcohol, it's going  
09:31:08 21 to go down. That's an acute phenomenon, that's not a chronic  
09:31:14 22 condition.

09:31:14 23 And that testimony, Your Honor, by the way, was  
09:31:15 24 not in the summary judgment record, either was this testimony  
09:31:19 25 from Dr. Peck who is Amarin's FDA regulatory expert. He

09:31:22 1 conceded that the indicated use of the Vascepa is not limited  
09:31:26 2 to chronic use. This goes to the heart of Your Honor's  
09:31:29 3 question.

09:31:30 4 FDA did not limit the indication to chronic use.  
09:31:34 5 It's a broad indication. It covers chronic patients if they  
09:31:39 6 need it, but it also covers the 20 percent or more of patients  
09:31:43 7 who just need a short term dose of icosapent.

09:31:50 8 So as Your Honor already found, Amarin's expert,  
09:31:53 9 Dr. Budoff, conceded the indication covers use for less than  
09:31:58 10 12 weeks, so, again, it's broad. Doctors can prescribe it for  
09:32:01 11 more than 12 weeks for sure, and they do, but they can also  
09:32:05 12 prescribe it for less.

09:32:06 13 And we think Dr. Budoff is right on this point.  
09:32:10 14 The only plausible way to read defendants' labels is that it  
09:32:16 15 leaves treatment duration entirely to the doctor's discretion.  
09:32:20 16 The label is complete indifferent as to duration of therapy.  
09:32:24 17 It leaves it up to the doctor to prescribe the drug for  
09:32:27 18 4 weeks, 8 weeks, 2 years, it doesn't matter, there is no  
09:32:31 19 preference in the label whatsoever, and there certainly is no  
09:32:35 20 instruction that doctors should prescribe the drug for at  
09:32:39 21 least 12 weeks.

09:32:40 22 And our expert, Dr. Sheinberg, will explain in  
09:32:45 23 more depth why defendants' labels do not recommend, encourage,  
09:32:48 24 promote, or otherwise require all -- each and every claim  
09:32:52 25 limitation, in particular the 12 weeks, and we point the Court



09:32:55 1 to the two Federal Circuit decisions from last year,  
09:33:00 2 *Grunenthal* and *Horizon*.

09:33:01 3 Now, turning to obviousness, there are lot of  
09:33:05 4 legal standards with regard to obviousness, and, for the most  
09:33:08 5 part, we're going to leave those to the briefing, but there's  
09:33:10 6 one legal standard I just want to focus on because it's very  
09:33:14 7 straightforward, it's simple, and it's well-established in  
09:33:16 8 Federal Circuit case law, and it relies on the *KSR* case from  
09:33:22 9 the US Supreme Court, and this is the standard.

09:33:24 10 "For an invention to be obvious to try, there  
09:33:25 11 must be a finite number of known choices in the prior  
09:33:29 12 art and a reasonable expectation of success with a  
09:33:32 13 choice that is tried."

09:33:33 14 Not a definite expectation, a reasonable  
09:33:36 15 expectation, and we submit the evidence will show it was at  
09:33:39 16 the very least obvious to try purified EPA in patients with  
09:33:44 17 severe hypertriglyceridemia to avoid LDL-C increases.

09:33:50 18 For example, if you start with the Lovaza  
09:33:53 19 product, this was an FDA approved product for the claimed  
09:33:55 20 method of treatment, very high triglycerides, 4 grams per day,  
09:33:58 21 the claim dose.

09:33:59 22 Lovaza label talks about two clinical trials,  
09:34:03 23 six weeks, 16 weeks, so, like Vascepa, it could be used for  
09:34:07 24 less than 12 weeks or more than 12 weeks. The only difference  
09:34:07 25 is that Lovaza, unlike the claims, includes the DHA component

09:34:17 1 of fish oil.

09:34:17 2 And as I mentioned at the beginning, in some  
09:34:20 3 patients Lovaza causes an increase in the bad cholesterol,  
09:34:24 4 this LDL-C, and we submit this warning in the Lovaza PDR  
09:34:30 5 raises a question that is incredibly obvious, and you don't  
09:34:35 6 need an M.D. to ask this question.

09:34:36 7 If you have an LDL side effect in a product that  
09:34:41 8 is two active ingredients, EPA and DHA, the obvious question  
09:34:47 9 is, is the side effect from only one of them, and there's a  
09:34:50 10 finite number of answers. It's either EPA causing the side  
09:34:54 11 effect, DHA, or both of them. Three options.

09:34:57 12 That would have been obvious to a skilled  
09:35:00 13 artisan, and the skilled artisan who have looked for prior art  
09:35:04 14 to see is there prior art that talks about whether LDL-C is  
09:35:04 15 associated with either DHA or EPA.

09:35:11 16 And a skilled artisan would have found this Mori  
09:35:14 17 reference. This Mori reference hits this dead on. The  
09:35:18 18 purpose of this clinical study was to see if there were  
09:35:21 19 different effects on lipids from DHA and EPA.

09:35:21 20 They used 4 grams of EPA, the claim dose,  
09:35:26 21 compared it to 4 grams of DHA in a 59-person trial, and the  
09:35:34 22 finding was that LDL cholesterol increased significantly with  
09:35:36 23 DHA but not with EPA.

09:35:39 24 And there are two other studies that counsel  
09:35:40 25 mentioned, Hayashi and Kurabayashi, and these are consistent

1 with Mori's findings because they both found that EPA had no  
2 statistically significant effect on LDL-C.

3 So as you'll see from Amarin's own documents,  
4 the only evidence out there is that EPA did not increase  
5 LDL-C. We don't know why, as counsel said, but the -- but the  
6 reasonable expectation was that if you take EPA, you're not  
7 going to get that side effect.

8 So it was, at a minimum, obvious to try the  
9 4-gram purified EPA dose in Mori for the Lovaza indication to  
10 see if you can reduce the triglycerides, which pure EPA does,  
11 without the Lovaza side effect. It's that simple. That's  
12 what the obviousness case is about.

13 Amarin makes a number of arguments. We didn't  
14 hear this one, but Amarin in the briefs disputes that it would  
15 be obvious to use the 4-gram dose. We find that argument  
16 remarkable because Mori itself used the 4-gram dose, and  
17 Amarin's expert concedes there are at least six prior art  
18 references showing that 4 grams pure EPA reduces  
19 triglycerides.

20 Amarin also argues that these studies mainly  
21 focus on patients who had triglycerides below 500, and that's  
22 not surprising, Your Honor, because it's rare to have  
23 triglycerides over 500. This is not a common occurrence.  
24 This is a rare condition, and it's extremely rare to have this  
25 genetic condition for severe hypertriglyceridemia.

09:37:11 1 But as you saw from the in limine briefing,  
09:37:15 2 Amarin made the same argument to the patent office and  
09:37:18 3 submitted the declaration of a statistician, Dr. Lavin, who  
09:37:22 4 mischaracterized the prior art and led the examiner to reach  
09:37:22 5 this finding in the notice of allowance.

09:37:29 6 "The prior art does not teach the  
09:37:30 7 administration of EPA to patients with triglycerides  
09:37:33 8 above 500."

09:37:34 9 That's what the examiner found, and everyone  
09:37:37 10 agrees now that that is not correct. Dr. Toth, Amarin's  
09:37:42 11 expert, concedes that purified EPA was used in the prior art  
09:37:47 12 to treat patients above 500. Amarin did not invent that  
09:37:51 13 method.

09:37:51 14 A skilled artisan had a reasonable expectation  
09:37:56 15 of success because each and every claim limitation was  
09:37:59 16 disclosed in the prior art, at least in one prior art  
09:38:03 17 reference, sometimes multiple references.

09:38:05 18 Now, to be sure, Amarin crafted its patent  
09:38:08 19 claims carefully to narrowly describe the method so that  
09:38:12 20 there's not one particular reference that happens to hit every  
09:38:16 21 single claim limitation. So counsel is right, this is not an  
09:38:19 22 anticipation case, but all the claims, all the asserted  
09:38:24 23 claims, were obvious.

09:38:25 24 Now, one of the arguments Amarin makes is that  
09:38:28 25 the prior art was before the examiner, but the examiner

1 found -- even despite the misrepresentation from Dr. Lavin,  
2 the examiner found that the prior art references led him to  
3 the conclusion that it will be obvious to treat patients  
4 having triglycerides above 500 with 96 percent pure EPA.

5 The examiner read the prior art the same we did.  
6 The examiner issued the patent only based on the secondary  
7 considerations, unexpected results and long-felt need, and as  
8 I'll explain in a moment, the examiner made mistakes.

9 Unexpected results, just to be clear, the  
10 examiner wasn't relying on REDUCE-IT, REDUCE-IT came later.  
11 The examiner relied on MARINE, and MARINE showed an  
12 8.5 percent reduction in apo B, it's a lipid marker.

13 But the examiner overlooked one of the  
14 references, Kurabayashi, which showed a seven percent  
15 reduction in apo B from pure EPA. So that apo B reduction was  
16 not an unexpected result.

17 The examiner also found a long-felt unmet need  
18 in view of the Lovaza warning that we talked about, but the  
19 examiner didn't appreciate -- keeping in mind, of course, this  
20 is an *ex parte* proceeding, the examiner didn't appreciate that  
21 in practice this LDL-C increase was routinely addressed with  
22 statins, and Amarin's own validity contentions concede this.

23 Lovaza was a blockbuster drug. This LDL-C  
24 increase was not in any way stopping doctors or patients from  
25 use being Lovaza. If there was an LDL-C increase, the

patients took a statin.

Now, there was still a motivation in the art, if you could avoid that LDL-C increase, you would.

So this gets us to REDUCE-IT, and there are two independent reasons for why REDUCE-IT is irrelevant. Already touched on the fact that the REDUCE-IT results were confirmatory, they confirmed the JELIS trial results.

Amarin argues that the JELIS study has numerous methodological flaws. This is contrary to what Amarin said in its internal documents to the FDA and to its investors.

Now, Amarin's point, to be fair, is that FDA didn't find that JELIS was sufficient to approve the new cardiovascular indication, and that is true. But the standards for FDA, as the case law, the *Allergan v Sando* makes clear, much, much higher than the standard for reasonable expectation of success. We have a reasonable expectation of success because of the *Lancet* article, the Yokoyama JELIS trial.

Just a few months ago Amarin is still telling the FDA that the REDUCE-IT results, the cardiovascular benefits, are consistent with JELIS, and we submit this *PharmaStem* case gets to the heart of issue. Scientific confirmation of what was already believed to be true may be a valuable contribution but it does not give rise to a patentable invention, and we submit that is this case is in a

09:41:42 1 nutshell.

09:41:42 2 REDUCE-IT is also irrelevant because there's no  
09:41:46 3 nexus to the claims. Regardless of JELIS, there's no nexus.  
09:41:51 4 The claims obviously require triglycerides over 500. The vast  
09:41:55 5 majority of prescriptions are for patients with triglycerides  
09:41:58 6 under 500. That's to continue to reduce triglycerides or  
09:42:03 7 because of the cardiovascular effects seen in JELIS and  
09:42:06 8 REDUCE-IT. That's the vast majority of prescriptions in this  
09:42:10 9 case, and it's probably going to go up now that there's a new  
09:42:13 10 indication.

09:42:14 11 REDUCE-IT, and this is important, Your Honor, is  
09:42:16 12 separately patented. Amarin has a lot of patents covering the  
09:42:20 13 REDUCE-IT method. The REDUCE-IT method is completely  
09:42:23 14 different from the claim method of reducing triglycerides.  
09:42:26 15 REDUCE-IT is not even focused on reducing triglycerides.

09:42:31 16 Leads me to my last point, your Honor, is that  
09:42:33 17 Amarin -- Amarin has four clinical experts, none of them are  
09:42:36 18 independent.

09:42:37 19 Here is an Amarin document talking about its  
09:42:40 20 speakers bureau, and these are three of their experts,  
09:42:44 21 Dr. Toth, Dr. Mason, Dr. Budoff; the fourth one, Dr. Ismail.  
09:42:48 22 They're all on Amarin's payroll, and they literally have  
09:42:52 23 received hundreds of thousands of dollars unrelated to this  
09:42:56 24 case.

09:42:56 25 And we think this is important because if the

09:42:58 1 experts come and take the stand and try to contradict the  
09:43:00 2 deposition testimony that we looked at, or they try to offer  
09:43:03 3 opinions that directly conflict with what Amarin said at the  
09:43:08 4 time, or to investors, or to the FDA we, submit that this lack  
09:43:13 5 of independence becomes very relevant.

09:43:15 6 All of our experts are independent.

09:43:20 7 And, with that, Your Honor, we submit that  
09:43:22 8 judgment should be entered for defendant on both the issues of  
09:43:26 9 noninfringement and obviousness.

09:43:29 10 Thank you.

09:43:30 11 THE COURT: Thank you.

09:43:35 12 All right. With that, we'll begin with -- I  
09:43:38 13 plan to take our morning break around -- in about 30 minutes  
09:43:42 14 or so, but perhaps we could begin with the first witness  
09:43:47 15 finally?

09:43:47 16 MS. KEANE: Your Honor, Meagan Keane on behalf  
09:43:50 17 of plaintiffs. The plaintiffs call Dr. Steve Ketchum.

09:44:14 18 And, Your Honor, while Dr. Ketchum is getting  
09:44:17 19 settled, we do have a witness binder for the witness as well  
09:44:20 20 as opposing counsel. Our understanding is that Your Honor  
09:44:23 21 would prefer not to have a witness binder, but we have extra  
09:44:27 22 copies if you would like.

09:44:28 23 THE COURT: Thank you.

09:44:28 24 MS. KEANE: May we approach and hand out the  
09:44:31 25 binders?



09:44:31 1 THE COURT: Yes.

2 MS. KEANE: Thank you.

3 STEVE KETCHUM,  
4 called as a witness on behalf of the Plaintiff,  
5 was sworn and testified as follows:

09:44:41 5 THE CLERK: Please be seated.

09:44:44 6 State for the record your full name and spell your  
09:44:55 7 last name.

09:44:55 8 THE WITNESS: My name is Steve Ketchum;  
09:45:01 9 S-t-e-v-e, K-e-t-c-h-u-m.

09:45:07 10 DIRECT EXAMINATION

09:45:07 11 BY MS. KEANE:

09:45:08 12 Q Good morning, Dr. Ketchum.

09:45:10 13 Dr. Ketchum, are you currently employed?

09:45:12 14 A Yes, I am.

09:45:13 15 Q Where are you currently employed?

09:45:15 16 A I'm employed at Amarin Pharma, Incorporated.

09:45:18 17 Q What is your position at Amarin?

09:45:20 18 A I'm a senior vice-president, president of research and  
09:45:28 19 development, and the chief scientific officer at Amarin.

09:45:28 20 Q What your responsibilities at Amarin?

09:45:29 21 A They encompass all of the technical disciplines that flow  
09:45:32 22 into drug development at Amarin, so that includes all the  
09:45:36 23 scientific disciplines, including chemistry, manufacturing,  
09:45:41 24 controls, regulatory affairs, clinical development, statistics  
09:45:47 25 and data management, and program management.

09:45:49 1 Q When did you join Amarin?

09:45:51 2 A I joined in February of 2012.

09:45:54 3 Q And could you briefly explain what is Amarin. Tell us  
09:45:58 4 about Amarin.

09:45:59 5 A So Amarin is a pharmaceutical company that's focused on  
09:46:03 6 developing cardiovascular therapies for unmet medical needs.

09:46:09 7 Q And does Amarin have any products?

09:46:11 8 A Yes, Amarin has one commercialized product.

09:46:14 9 Q And what is that product?

09:46:15 10 A Its name is Vascepa Icosapent Ethyl Capsules.

09:46:21 11 Q Are you familiar with the regulatory history of Vascepa?

09:46:24 12 A Yes. My responsibilities at Amarin encompass the  
09:46:28 13 regulatory domain so I am familiar with the regulatory  
09:46:31 14 aspects.

09:46:32 15 Q And after you joined Amarin in 2012, did you do anything  
09:46:35 16 to familiarize yourself with the regulatory history of Vascepa  
09:46:40 17 prior to your time at the company?

09:46:41 18 A Yes. So I was recruited into Amarin in the middle of the  
09:46:47 19 original NDA review clock for Vascepa, specifically brought in  
09:46:52 20 based on my development and regulatory expertise.

09:46:56 21 So one of the first aspects I did upon joining the  
09:47:00 22 company was ensure that I was familiar with that regulatory  
09:47:03 23 background with the original NDA application that had been  
09:47:09 24 submitted to FDA and the history leading up to that point in  
09:47:13 25 time.

09:47:13 1 Q Are you also familiar with the clinical development of  
09:47:17 2 Vascepa?

09:47:17 3 A Yes, I am. Again, in my role at Amarin I was brought in  
09:47:24 4 to head up clinical research and development, and so I needed  
09:47:28 5 to familiarize myself with both the completed studies and any  
09:47:34 6 other studies that were designed and underway.

09:47:38 7 Q What is the active ingredient in Vascepa?

09:47:41 8 A The active ingredient, its generic name is icosapent  
09:47:41 9 ethyl, and what it is, it's an ethyl ester form of a highly  
09:47:41 10 purified -- a purified form of eicosapentaenoic acid or EPA  
09:47:41 11 which is an omega-3 acid.

09:47:45 12 Q And what do you mean by highly purified?

13 A What I mean is that Vascepa and icosapent ethyl, the  
14 product is sourced, originally sourced, from fish derived  
15 material which contains a range of omega-3s, omega-6 and other  
16 chemical compounds in it just naturally, and to obtain the  
17 single entity, highly purified EPA you have to do a series of  
18 basically manufacturing steps, purifications, distillations,  
09:48:01 19 in order to remove those non-EPA compounds.

09:48:01 20 Q Is Vascepa approved in the U.S.?

09:48:46 21 A Yes. Vascepa is approved in the United States.

09:48:50 22 Q And what conditions is Vascepa approved to treat?

09:48:53 23 A It's currently approved for two different indications.

09:48:58 24 The first indication was approved in July of 2012 as  
09:49:05 25 an adjunct to diet to reduce triglycerides in adult patients

09:49:11 1 with severe hypertriglyceridemia, and that means that the  
09:49:16 2 patients had triglycerides levels greater than or equal to  
09:49:19 3 500 milligrams per deciliter.

09:49:22 4 And then more recently, in December of 2019, Vascepa  
09:49:26 5 was approved as an adjunct to maximally tolerate its statin  
09:49:32 6 therapy to reduce cardiovascular risk in adult patients with  
09:49:38 7 elevated triglycerides characterized by triglyceride levels  
09:49:43 8 greater than or equal to 150 milligrams per deciliter, and  
09:49:48 9 those patients had other risk factors for cardiovascular  
09:49:53 10 disease.

09:49:53 11 Q Why was Vascepa developed?

09:49:54 12 A Vascepa was developed to address a number of unmet  
09:50:00 13 medical needs.

09:50:01 14 Q And what are those unmet medical needs?

09:50:04 15 A They're the unmet medical needs that are -- ultimately  
09:50:10 16 led to the indications that I just described.

09:50:13 17 So the first was in patients with severe  
09:50:20 18 hypertriglyceridemia. There are number of other treatment  
09:50:22 19 options, but the unmet medical need was developing Vascepa to  
09:50:32 20 achieve those robust triglyceride reductions that are the  
09:50:36 21 primary lipid abnormality in those patients, but to do so  
09:50:41 22 without increasing LDL-C, which is bad cholesterol, and to do  
09:50:46 23 so in a way that had a favorable side effect profile that was  
09:50:53 24 differentiated from some of those existing products.

09:50:56 25 Q And did Vascepa successfully meet this need?

09:50:59 1 A Yes. In the study that we called MARINE, we showed that  
09:51:04 2 the product could achieve those objectives.

09:51:07 3 Q And you mentioned there was a second need as well, and  
09:51:10 4 what need was that?

09:51:11 5 A Yeah, so, the other unmet medical need, so the statin  
09:51:18 6 class of drugs which address LDL-C or bad cholesterol were  
09:51:24 7 certainly important advances in medical science and had been  
09:51:29 8 shown to reduce cardiovascular risk to something on the order  
09:51:35 9 of 25 to 35 percent.

09:51:39 10 But cardiovascular disease continues to be a very  
09:51:43 11 major medical problem in the United States and elsewhere,  
09:51:46 12 essentially a leading cause of death and morbidity and cost to  
09:51:52 13 the healthcare system, and so it was an unmet medical need for  
09:51:57 14 a product that could be added on top of a statin to address  
09:52:01 15 that residual risk.

09:52:03 16 And so our goal at Amarin was to address that unmet  
09:52:08 17 medical need by demonstrating that Vascepa could be added on  
09:52:15 18 top of the statin, of course, without negating the effect of  
09:52:20 19 the statin, which was important on it's own to reduce some  
09:52:25 20 level of residual cardiovascular risk, and to show that it  
09:52:29 21 would be an incremental benefit of adding Vascepa in terms of  
09:52:33 22 additional cardiovascular risk reduction and to do so in a  
09:52:36 23 safe and tolerable manner.

09:52:40 24 Q And was Vascepa successful in meeting that need?

09:52:42 25 A Yes. The REDUCE-IT study showed that it achieved those

09:52:46 1 objectives.

09:52:47 2 Q Could you describe for us Amarin's culture as a company.

09:52:50 3 A Yes. Amarin, certainly in the window of time when I  
09:52:55 4 joined the company and prior to that, is a small company,  
09:52:58 5 literally dozens of individuals as opposed to hundreds of  
09:53:04 6 thousands. So a small innovative company, science driven,  
09:53:09 7 very much focused -- as opposed to having a broad portfolio  
09:53:14 8 where the individuals' time and scientific attention was split  
09:53:18 9 across multiple projects and multiple molecules, was very much  
09:53:23 10 focused on the science of EPA, and driving that forward  
09:53:27 11 required a lot of focus, so I'd say we're both a very focused,  
09:53:34 12 disciplined company.

09:53:35 13 It's always true that drug development takes long  
09:53:39 14 periods of time, and so I would say we've had to display a lot  
09:53:44 15 of patience and perseverance over time.

09:53:47 16 Q How long has Amarin been focused on developing Vascepa?

09:53:52 17 A So for the unmet medical needs that I mentioned earlier  
09:53:58 18 in terms of severe hypertriglyceridemia and cardiovascular  
09:54:02 19 risk reduction, we've been focused for those for a decade  
09:54:07 20 plus, so for ten plus years.

09:54:07 21 Q And how much was Amarin invested in developing Vascepa?

09:54:12 22 A Approximately \$500 million on those programs across the  
09:54:16 23 decade-plus time.

09:54:16 24 Q And during the development of Vascepa did Amarin face any  
09:54:20 25 scientific challenges?

09:54:22 1 A Yes. Drug development is always fraught with challenges.  
09:54:28 2 We had more than our number of technical challenges across the  
09:54:34 3 years.

09:54:37 4 So we had some lofty goals in trying to address  
09:54:41 5 these unmet medical needs, and, first, before being able to  
09:54:45 6 advance the clinical trials, we had to put together an  
09:54:48 7 extensive vendor network to actually go through the steps that  
09:54:52 8 I mentioned earlier about obtaining a highly purified single  
09:54:56 9 entity EPA product that could be manufactured reliably,  
09:55:02 10 consistently, and in a dosage form that would protect its  
09:55:06 11 stability across, you know, a sufficient length of time to  
09:55:11 12 supply clinical trials and ultimately to have commercial  
09:55:14 13 viability. So that was one domain of technical challenge.

09:55:18 14 And then we, as sponsors are generally required to  
09:55:22 15 do, we had to progress some nonclinical and early clinical  
09:55:27 16 work. Each of those had their own challenges in terms of  
09:55:30 17 assembling, you know, the right vendor network with the right  
09:55:35 18 skill sets and experience to perform the work professionally  
09:55:39 19 and at a high quality to the standards required by FDA and  
09:55:44 20 other bodies.

09:55:44 21 And then clinically, we had to assemble a vendor  
09:55:49 22 network again that spanned across the whole development  
09:55:57 23 program more than 11 countries and hundreds of sites, and  
09:56:00 24 assemble, you know, the people who could progress the work  
09:56:04 25 across those domains.

09:56:05 1 So, yes, many technical challenges across the years.

09:56:09 2 Q And has Amarin faced challenges entering the  
09:56:12 3 cardiovascular space?

09:56:14 4 A You know, so each disease area presents its own  
09:56:19 5 challenges. The cardiovascular metabolic space, because as  
09:56:25 6 compared to, for example, some other areas that might be  
09:56:29 7 considered ultra orphan or rarer diseases, we're talking  
09:56:34 8 about, you know, fairly substantially sized patient  
09:56:39 9 populations ultimately when you look -- add to the business  
09:56:40 10 objective of bringing a product to fulfill that unmet medical  
09:56:45 11 need.

09:56:45 12 So, classically, I'd say the cardio-metabolic space  
09:56:50 13 has been a place for larger pharma, with a multinational  
09:56:53 14 presence with the capabilities to conduct the large long-term  
09:56:58 15 cardiovascular outcome studies in -- whether it be diabetes  
09:57:03 16 or, you know, cardiovascular risk reduction.

09:57:06 17 So, yes, as a very small player, trying to assemble  
09:57:10 18 that network, trying to raise the financial capital needed to  
09:57:16 19 conduct the work, we did face a host of challenges.

09:57:22 20 Q So I'd like you to talk a little bit about your  
09:57:25 21 background specifically. Can you just tell us a little bit  
09:57:27 22 about your educational background.

09:57:29 23 A Yes. So I have a Bachelor of Science degree in  
09:57:32 24 biological sciences from Stanford University, and a Ph.D. in  
09:57:37 25 pharmacology from University College London.



09:57:41 1 Q What is pharmacology?

09:57:43 2 A Pharmacology is basically a field of science that studies  
09:57:46 3 how medicines work in the body.

09:57:48 4 Q And what did you do after graduating from the University  
09:57:53 5 College London?

09:57:53 6 A So my Ph.D fellowship was funded by a Swiss company,  
09:57:58 7 Sandos Pharmaceuticals, and I then went on to do a  
09:58:01 8 postdoctoral fellowship in Switzerland but for the British  
09:58:08 9 company GlaxoSmithKline.

09:58:08 10 Q And what did you do after your postdoc?

09:58:11 11 A I was recruited to Serono Pharmaceuticals at their  
09:58:17 12 headquarters in Geneva, Switzerland. I was hired in for my  
09:58:24 13 pharmacology and molecular biology expertise to help progress  
09:58:27 14 their early phase programs with two recombinant fertility  
09:58:33 15 hormones in their international regulatory affairs group.

09:58:35 16 Q What do you mean by regulatory affairs?

09:58:38 17 A By regulatory affairs, it's basically a discipline within  
09:58:43 18 the pharmaceutical industry that's responsible for assembling  
09:58:49 19 documentation for interacting with development teams to ensure  
09:58:53 20 that as they progress their work, that they're doing so  
09:58:57 21 consistent with regulatory guidances or laws, depending upon  
09:59:03 22 the country, and the goals of that particular project.

09:59:10 23 So my role was involved in helping teams to progress  
09:59:14 24 towards the original investigational new drug application and  
09:59:19 25 progress the clinical trial work in the U.S. and major markets

09:59:25 1 like Japan and Europe.

09:59:27 2 Q And what did you do after your work at Serono?

09:59:30 3 A After Serono I was recruited to join an American firm  
09:59:36 4 based in Northern California, Alza Pharmaceuticals, to join  
09:59:41 5 their regulatory affairs group and progress a number of their  
09:59:45 6 projects through the development process.

09:59:48 7 Q Okay. And when you refer to a development process, could  
09:59:52 8 you briefly explain what you're referring to?

09:59:54 9 A Yes. So, at each of these, whether it be Serono or Alza  
10:00:00 10 and subsequently, my role was to work with teams starting with  
10:00:05 11 the chemistry manufacturing control teams to progress the  
10:00:10 12 manufacture of the clinical trial material and to describe it  
10:00:14 13 in documents that needed to be submitted.

10:00:17 14 I'll just for simplicity sake speak to the U.S. FDA.  
10:00:22 15 So I would work with teams to assemble chemistry manufacturing  
10:00:28 16 controls, nonclinical and clinical information, to open up an  
10:00:33 17 original IND application.

10:00:36 18 And the classic phases are, you know, you go through  
10:00:40 19 that formulation development, and then you generally need to  
10:00:44 20 progress some preclinical study support to support moving into  
10:00:49 21 humans, and then you progress through various phases  
10:00:54 22 classically.

10:00:55 23 So phase one is classically in healthy -- otherwise  
10:00:59 24 healthy human volunteers to administer, you know, the dosage  
10:01:04 25 form and to follow its pharmacokinetics typically across some

1 type of a dose range to get idea of how the drug is behaving  
2 in the body, how it's being metabolized, et cetera.

3 And then classically, over time one moves to phase 2  
4 to conduct early proof of -- what's called early proof of  
5 principle studies. So in those studies you're again testing  
6 generally a number of doses of the study drug, and you're  
7 looking at at least preliminary indicators of effectiveness  
8 and safety.

9 And then -- and then once a sponsor feels they have  
10 sufficient information and generally that the regulatory  
11 authority agrees, you would progress into the pivotal phase of  
12 drug development, or phase three, where you're generally  
13 conducting larger, longer term trials.

14 Sometimes single trials will suffice, other times  
15 you have to perform multiple trials, and you're generating the  
16 pivotal basis for the determination of effectiveness and  
17 safety for a particular indication.

18 Q So turning back to your background, after Alza what did  
19 you do next?

20 A So Alza, after working and helping to progress three --  
21 principally three products through to commercialization, and  
22 the company was acquired by Johnson & Johnson, and a number of  
23 the scientists and senior management moved on, so I was  
24 recruited to join -- by the former CEO of Alza to join  
25 Interbiotics Pharmaceuticals as their vice-president of

1 regulatory affairs.

2 Q And after Interbiotics, what did you do next?

3 A After Interbiotics that same former CEO of Alza at that  
4 point in time had become the CEO of Reliant Pharmaceuticals in  
5 New Jersey, so he and his team recruited me away to join them  
6 to become head of R&D at Reliant Pharmaceuticals.

7 Q And did your position at Reliant change over time?

8 A Yes, I initially was a senior vice-president and head of  
9 R&D, and my role a year or so into expanded to include the  
10 medical affairs function.

11 Q And how did your position while you were at Reliant  
12 compare to the previous positions that you held?

13 A So it was -- it also encompassed the regulatory affairs  
14 domain which was similar to my role at Interbiotics. It was  
15 similar in that I also had responsibilities for the chemistry,  
16 manufacturing, and controls, and some of quality assurance  
17 functions.

18 The key difference was that I had a responsibility  
19 at Reliant for the clinical research and development and  
20 program management and those functions.

21 Q Were you responsible for any products during your time at  
22 Reliant?

23 A Yes. So Reliant had a larger portfolio than some of the  
24 prior companies I'd been with. So upon joining I had  
25 responsibility for an a Fenofibrate product called Antara,

1 which was in the company's portfolio, along with an atrial  
2 fibrillation agent called Rhythmol SR. They had a number of  
3 antihypertensive medications, including some controlled  
4 release dosage form versions, and they had a statin.

5 And then I was really brought in to help launch a  
6 newly licensed asset from Abbott Parmaceuticals which at the  
7 time was called Omacor, it's an omega-3 acid ethyl esters  
8 product that had been approved in late 2004 for severe  
9 hypertriglyceridemia, and I was brought in in May of 2005 to  
10 help the team progress towards launch of that product in --  
11 within -- later within 2005.

12 That product, its name ultimately needed to be  
13 changed to Lovaza.

14 Q And what specifically is Lovaza?

15 A So Lovaza is a soft gelatin capsule formulation of  
16 omega-3 acid ethyl esters which is basically a mixture of a  
17 number of omega-3 fatty acids.

18 Q And how does the composition of Lovaza compare to  
19 Vascepa?

20 A So, again, Lovaza is a complex mixture, so it has two  
21 predominant omega-3 moieties that are, you know,  
22 eicosapentaenoic acid EPA and docosahexaenoic acid or DHA, and  
23 has other minor omega-3 or omega-6 species that are in that  
24 mixture.

25 And so to differentiate it from Vascepa, Vascepa is

10:06:25 1 a highly purified single entity agent consisting only of EPA.

10:06:31 2 Q How long did you work for Reliant?

10:06:33 3 A I worked for Reliant for three years. About a little  
10:06:39 4 over two, two-and-a-half years in, the company was acquired by  
10:06:44 5 GlaxoSmithKline, and I remained with the organization to  
10:06:50 6 efficiently transfer all the commercialized products and  
10:06:53 7 ongoing clinical trials and regulatory activities to that  
10:06:57 8 organization, and then I was ready to transition elsewhere.

10:07:01 9 Q And what years were you -- what was the time frame when  
10:07:04 10 you were at Reliant?

10:07:05 11 A I was at Reliant from May of 2005 through May of 2008.

10:07:10 12 Q And after Reliant, where were you employed?

10:07:14 13 A So I was recruited by some former Alza colleagues to  
10:07:21 14 rejoin them back out in Northern California, and they hired me  
10:07:25 15 in to become their head of R&D at a small oncology focused  
10:07:30 16 company called Sunesis Pharmaceuticals.

10:07:34 17 Q And how long were you with Sunesis?

10:07:37 18 A I was with Sunesis from essentially May of 2008  
10:07:43 19 through -- up to the time of joining Amarin in February of  
10:07:46 20 2012.

10:07:47 21 Q Okay. So, Dr. Ketchum, I would like to talk a little bit  
10:07:52 22 more about Vascepa. If we could turn to -- if we could turn  
10:07:55 23 to Plaintiff's Exhibit 1186 in your binder.

10:08:03 24 And, Mr. Brooks, if we could --

10:08:06 25 MS. KEANE: Oh, Ms. Vannozzi, could we switch --

10:08:13 1 thank you.

10:08:22 2 THE COURT: Did you say 1186?

10:08:24 3 MS. KEANE: 1186, yes.

10:08:36 4 BY MS. KEANE:

10:08:39 5 Q Dr. Ketchum, do you recognize Plaintiff's Exhibit 1186?

10:08:44 6 A Yes, I do.

10:08:45 7 Q And what is Plaintiff's Exhibit 1186?

10:08:48 8 A That exhibit is the approved prescribing information for  
10:08:54 9 Vascepa as of December 2019.

10:09:01 10 MS. KEANE: Your Honor, plaintiffs move to admit  
10:09:03 11 Plaintiff's Exhibit 1186 into evidence.

10:09:06 12 MR. KLEIN: No objection.

10:09:09 13 THE COURT: Exhibit 1186 is admitted.

10:09:09 14 (Plaintiff's Exhibit 1186 received in  
10:09:12 evidence.)

10:09:12 15 BY MS. KEANE:

10:09:12 16 Q So, Dr. Ketchum, could you first explain to us what an  
10:09:17 17 indication is.

10:09:18 18 A Yes. An indication is an approved medical use for a  
10:09:24 19 pharmaceutical product.

10:09:26 20 Q Could you direct us to where Vascepa's indications are  
10:09:31 21 reflected in Exhibit 1186?

10:09:33 22 A Yes. The approved indications are reflected in a number  
10:09:37 23 of places within the approved prescribing information.  
10:09:41 24 Firstly, there within the highlight section, under the heading  
10:09:45 25 Indications and Usage. Also within the full prescribing

1 information within section 1.

2 MS. KEANE: And, Mr. Brooks, if you could pull  
3 up section 1 on page 2.

4 BY MS. KEANE:

5 Q And what is the first indication that's listed for  
6 Vascepa?

7 A So the first indication is:

8 "As an adjunct to maximally tolerated statin  
9 therapy to reduce the risk of myocardial infarction,  
10 stroke, coronary revascularization, and unstable  
11 angina requiring hospitalization in adult patients  
12 with elevated triglyceride (TG) levels greater or  
13 equal to 150 milligrams per deciliter, and  
14 established cardiovascular disease or diabetes  
15 mellitus and two or more additional risk factors for  
16 cardiovascular disease."

17 Q And is this first indication based on the results of a  
18 particular clinical trial?

19 A Yes, there -- on the basis of the REDUCE-IT large  
20 long-term cardiovascular outcomes trial.

21 Q Okay. So for ease of reference today, is it okay if we  
22 refer to this first indication as the REDUCE-IT indication?

23 A Yes.

24 Q Dr. Ketchum, what is Vascepa's second indication?

25 A



10:11:09 1 A "As an adjunct to diet to reduce TG levels in  
10:11:13 2 adult patients with severe (greater than or equal to  
10:11:16 3 500 milligrams per deciliter) hypertriglyceridemia."

10:11:22 4 Q And for -- and is the second indication based on a  
10:11:27 5 particular clinical trial?

10:11:28 6 A Yes. The pivotal basis for that indication was on the  
10:11:34 7 basis of what we refer to as the MARINE trial.

10:11:37 8 Q Okay. For purposes of your testimony today, is it okay  
10:11:40 9 if we refer to this indication as the MARINE indication?

10:11:44 10 A Yes.

10:11:44 11 Q When was Vascepa first approved?

10:11:46 12 A Vascepa was first approved in July of 2012.

10:11:50 13 Q Has Vascepa always been approved for both of these two  
10:11:54 14 indications?

10:11:54 15 A No. No, it is not.

10:11:56 16 Q And with -- with respect to the original approval of  
10:12:01 17 Vascepa, what was the approved indication?

10:12:04 18 A The original approval in July 2012 was for that second  
10:12:10 19 indication that I read in the severely hypertriglyceridemic  
10:12:16 20 patient population.

10:12:17 21 Q And when was the REDUCE-IT indication approved?

10:12:19 22 A In December 2019.

10:12:21 23 Q Did -- was there a different labeling associated with  
10:12:25 24 Vascepa prior to 2019?

10:12:27 25 A Yes.

10:12:29 1 Q If we could turn to Plaintiff's Exhibit 940.

10:12:37 2 MS. KEANE: And, Your Honor, I'll note for the  
10:12:38 3 record that Plaintiff's Exhibit 940 is actually on the list of  
10:12:42 4 admitted exhibits.

10:12:44 5 THE COURT: Thank you.

10:12:45 6 BY MS. KEANE:

10:12:45 7 Q Dr. Ketchum, what is Exhibit 940?

10:12:48 8 A Exhibit 940 is the approved prescribing information for  
10:12:54 9 Vascepa dated February of 2017.

10:12:58 10 Q And if we could turn to page 2 and take a look at the  
10:13:03 11 Indications section. And where is the initial indication for  
10:13:13 12 Vascepa reflected?

10:13:14 13 A On this portion of the full prescribing information, it's  
10:13:19 14 in section 1, Indications and Usage, in the first sentence.

10:13:23 15 Q And at a high level can you explain the differences  
10:13:28 16 between Plaintiffs' Exhibit 940 and Plaintiffs' Exhibit 1186.

10:13:33 17 A So Exhibit 940 is focused on the information --  
10:13:42 18 prescribing information for the first approved indication.  
10:13:47 19 And the prior exhibit is focused on the -- the revised  
10:13:53 20 approved prescribing information that reflects the addition of  
10:13:57 21 the expanded indication for -- based on the REDUCE-IT trial  
10:14:02 22 results.

10:14:02 23 And so that section that I read would have changed  
10:14:07 24 between the two labels along with other sections that are  
10:14:12 25 relevant to a description of the REDUCE-IT trial results or

10:14:18 1 other information associated with the trial.

10:14:20 2 Q And if we could turn back to --

10:14:23 3 MS. KEANE: Mr. Brooks, if you turn back to  
10:14:25 4 Plaintiff's Exhibit 1186. Okay. And if we could highlight  
10:14:30 5 the MARINE indication.

10:14:30 6 BY MS. KEANE:

10:14:33 7 Q Dr. Ketchum, the MARINE indication refers to adjunct to  
10:14:38 8 diet. What does an adjunct to diet mean?

10:14:42 9 A It means in addition to a diet.

10:14:44 10 Q Okay. And with respect to the MARINE indication, is  
10:14:49 11 Vascepa indicated as AN adjunct to any other drug therapy?

10:14:54 12 A No. No. It's a monotherapy phrasing for an indication.

10:14:59 13 Q What is Vascepa's dosage form?

10:15:03 14 A The dosage form is -- appears in the full prescribing  
10:15:09 15 information in section 3, and, as I mentioned earlier, Vascepa  
10:15:14 16 is a soft gelatin capsule, and it's described within that  
10:15:19 17 section 3.

10:15:20 18 Q If we could turn to section 3. And where -- where is the  
10:15:27 19 dosage form reflected?

10:15:29 20 A So it's reflected there in the two bulleted elements,  
10:15:34 21 describes that it's available in both a 0.5-gram capsule and a  
10:15:41 22 one gram capsule. They're both Amber colored. One is oval,  
10:15:46 23 one is oblong. Both are soft-gelatin capsules, and they have  
10:15:51 24 different imprinting so that the two dosage forms can be  
10:15:53 25 distinguished.

10:15:54 1 Q What is the dosage strength for the Vascepa?

10:15:58 2 A So the dosage strength is either 0.5 grams or 1 gram.

10:16:03 3 Q And is the dosage strength also reflected in the  
10:16:06 4 labeling?

10:16:07 5 A Yes. The dosage strength is indicated within that same  
10:16:11 6 section 3.

10:16:12 7 Q How much of the active ingredient of icosapent ethyl is  
10:16:12 8 in each one-gram capsule of Vascepa?

10:16:19 9 A It involves a one-gram fill of icosapent ethyl.

10:16:24 10 Q And where is the fill weight of the capsules reflected in  
10:16:29 11 the labeling?

10:16:29 12 A So it appears in a later section in the label in  
10:16:34 13 section 11 in the description section of the describing  
10:16:41 14 information.

10:16:42 15 MS. KEANE: Mr. Brooks, if we could turn to  
10:16:44 16 section 11.

10:16:48 17 BY MS. KEANE:

10:16:48 18 Q Could you show us where the fill weight is reflected in  
10:16:52 19 the section 11?

10:16:53 20 A Yes, it's in the -- in the beginning of the second  
10:16:56 21 paragraph there where it says that each Vascepa capsule  
10:16:59 22 contains either 0.5 grams or 1 gram of icosapent ethyl in the  
10:17:08 23 respective capsule.

10:17:09 24 Q And what is the daily dose of Vascepa?

10:17:11 25 A So the total daily dose that's approved for Vascepa is 4

10:17:16 1 grams per day.

10:17:17 2 Q And where is the total dose of Vascepa reflected?

10:17:20 3 A So the total dose of the Vascepa appears back in  
10:17:26 4 section 2.2 in the Dosage and Administration section.

10:17:32 5 Q Could you direct us to where the dosage -- the daily dose  
10:17:43 6 of the Vascepa is indicated?

10:17:45 7 A Yes, in the first bulleted element under section 2.2  
10:17:50 8 states,

10:17:50 9 "The daily dose of Vascepa is 4 grams per day  
10:17:53 10 taken as either: Four 0.5-gram capsules twice daily  
10:17:59 11 with food; or as two 1 gram capsules twice daily with  
10:18:04 12 food."

10:18:04 13 Q Okay. What is the route of administration for Vascepa?

10:18:07 14 A The route -- it's an oral capsule that, as reflected in  
10:18:11 15 this second bullet, is intended to be swallowed whole, not to  
10:18:17 16 be broken open, crushed, dissolved, or chewed.

10:18:21 17 Q Thank you. So, Dr. Ketchum, I would like to turn to some  
10:18:25 18 other subjects, but I --

10:18:27 19 MS. KEANE: Your Honor, I would like to turn to  
10:18:30 20 a few other subjects. They wanted to talk about some  
10:18:33 21 terminology before we get into a further discussion.

10:18:36 22 THE COURT: And perhaps before you turn to the  
10:18:38 23 next subject it may be -- let me know when it's a good point  
10:18:43 24 to take our morning recess.

10:18:45 25 MS. KEANE: Now would be fine, Your Honor.

10:18:46 1 THE COURT: All right. We'll take our recess  
10:18:48 2 for about 15 minutes then.

10:18:49 3 Thank you.

10:18:49 4 (A recess was taken.)

10:39:48 5 THE COURT: Please be seated.

10:39:49 6 Ready to proceed?

10:39:50 7 MS. KEANE: Yes, I'm ready.

10:39:53 8 BY MS. KEANE:

10:39:54 9 Q So, Dr. Ketchum, before the break, we were about to talk  
10:39:56 10 about some terminology related to your testimony today. Do  
10:40:02 11 you have an understanding of what lipids are?

10:40:05 12 A Yes, I do.

10:40:06 13 Q What are lipids?

10:40:07 14 A So lipids are an organic class of compounds that include  
10:40:11 15 fatty acids and their derivatives.

10:40:15 16 Q And are you also familiar this triglycerides?

10:40:17 17 A Yes, I am.

10:40:19 18 Q What are triglycerides?

10:40:20 19 A So triglycerides are fats that exist in your blood, and  
10:40:25 20 it can be used for energy storage is one of their purposes.

10:40:30 21 Q Are you familiar with hypertriglyceridemia?

10:40:33 22 A Yes, I am.

10:40:34 23 Q What is hypertriglyceridemia?

10:40:37 24 A It basically just means high triglyceride levels.

10:40:40 25 Q And are there different levels of hypertriglyceridemia?

10:40:44 1 A Yes, there are. There's various scientific publications  
10:40:52 2 and documents that have characterized essentially normal  
10:40:57 3 levels of those fats in your blood as 150 milligrams per  
10:41:03 4 deciliter and below.

10:41:05 5 People can be considered borderline high if they're  
10:41:09 6 in the range of 150 to 199 milligrams per deciliter. They  
10:41:16 7 then get into the range of hypertriglyceridemia. High is  
10:41:22 8 classically characterized as 200 to 499 milligrams per  
10:41:28 9 deciliter. And then if the TG levels in the blood are very  
10:41:31 10 high or severely high, that's greater than or equal to  
10:41:39 11 500 milligrams per deciliter.

10:41:39 12 Q Okay. And the guidelines that you referred to, what  
10:41:41 13 guidelines are you referring to?

10:41:43 14 A I was referring to the National Cholesterol Education  
10:41:48 15 Program, or NCEP at ATP3 guidance.

10:41:53 16 Q Do you know how patients with severe hypertriglyceridemia  
10:41:57 17 are treated?

10:41:58 18 A Yes. So these -- so this is a chronic asymptomatic  
10:42:07 19 condition. It's -- what I mean by that is a patient cannot  
10:42:11 20 feel their triglycerides or these levels of fat in their  
10:42:16 21 blood. They can't feel if they're normal or abnormal.

10:42:20 22 And so people are essentially diagnosed with severe  
10:42:26 23 hypertriglyceridemia by having their blood lipids measured,  
10:42:30 24 and then, if they're determined to be severely  
10:42:33 25 hypertriglyceridemic, they can -- in addition to lifestyle

10:42:39 1 aspects such as making sure they're on a healthy diet, that  
10:42:43 2 they're exercising, they can be placed pharmacotherapy or drug  
10:42:49 3 therapy.

10:42:50 4 Q And why is it that triglycerides levels in these patients  
10:42:55 5 need to be reduced?

10:42:56 6 A So the -- so the medical condition of those excessively  
10:43:01 7 high triglycerides levels can lead to acute pancreatitis which  
10:43:09 8 is referring to the internal organ, the pancreas, and an  
10:43:17 9 inflammation basically that can result from the pancreas  
10:43:21 10 that's acute, meaning that it needs, it needs attention, that  
10:43:26 11 it can actually -- the triglycerides can build up, and it can  
10:43:30 12 actually lead to the need to go to the emergency room and can  
10:43:34 13 have some significant medical consequences.

10:43:37 14 Q So let's turn to the clinical development of Vascepa.  
10:43:41 15 During development was Vascepa known by any other name?

10:43:46 16 A During its clinical development there was a code  
10:43:49 17 identifier, AMR 101. Certain documents would also just  
10:43:55 18 simplify referring to it as, you know, containing EPA.

10:44:02 19 Q Can you, at a high level, describe the clinical  
10:44:06 20 development program for Vascepa.

10:44:09 21 A Yes. So the clinical development program that was put in  
10:44:14 22 place to address those unmet medical needs that I mentioned  
10:44:17 23 earlier is basically a three-part clinical development  
10:44:22 24 program.

10:44:22 25 The first study that was intended to address the



1 unmet medical need in severe hypertriglyceridemia we refer to  
2 as the MARINE trial. That was a 12-week -- had a 12-week  
3 randomized, double-blind, placebo-controlled, lipid-focused  
4 component, and a 40-week open label extension component to  
5 that trial.

6 A second trial -- so that was in a severely  
7 hypertriglyceridemic patient population. The second trial was  
8 focused in patients who were on statin therapy to control  
9 their bad cholesterol, their LDL, but in spite of that statin  
10 therapy had elevated triglycerides or high triglycerides in  
11 the range of 200 to 499 milligrams per deciliter. That,  
12 again, was a 12-week, lipid-focused trial.

13 And the third trial was a large, long term  
14 cardiovascular outcomes trial looking at Vascepa on top of  
15 statin therapy in patients with elevated triglycerides in the  
16 range of 150 to 499 milligrams per deciliter and who had other  
17 CV, cardiovascular disease risk factors.

18 Q And were all three of these studies successful?

19 A Yes, all three studies were successful in meeting their  
20 pre-specified primary endpoints and showing a safe and  
21 tolerable profile.

22 Q So let's turn to the timeline relating to the clinical  
23 development program. When did Amarin first approach FDA about  
24 its clinical development program?

25 A Amarin first approached FDA in the spring of 2008 to

1 discuss the proposed development program for those trials and  
2 those proposed indications.

3 Q And how -- how was it that Amarin approached the FDA?

4 A The R&D regulatory team reached out to the relevant  
5 review division at FDA, the Division of Metabolism -- or,  
6 excuse me, Metabolic and Endocrinology Drug Products, also  
7 referred to as DMEP, and indicated a desire to meet.

8 And as is typical in that situation, the sponsor  
9 then fills out a formal meeting request. In this case, they  
10 filled out what's called a meeting request for a type B  
11 pre-IND interaction.

12 Q And, Dr. Ketchum, if you could turn to exhibit --  
13 Plaintiff's Exhibit 482 in your binder.

14 MS. KEANE: And, Your Honor, I would just like  
15 to note for the record this is one of the exhibits that my  
16 colleague referenced earlier that we would like the  
17 opportunity to redact before it is included in the public  
18 record. But for purposes of today's testimony, I don't expect  
19 to get into anything that would require sealing the courtroom.

20 THE COURT: Thank you.

21 BY MS. KEANE:

22 Q So, Dr. Ketchum, if you could turn to Exhibit 482. It's  
23 put up on the screen. And 482 is a compilation of documents;  
24 is that right?

25 A Yes, it's a series of communications.

10:47:55 1 Q Okay. And if we could start with the document on page 1.

10:48:00 2 What is the document that begins on page 1?

10:48:03 3 A So the document that begins on page 1 is a letter from a  
10:48:10 4 party acting on behalf of Amarin to the Director of DMEP  
10:48:23 5 requesting -- formally requesting a pre-IND meeting.

10:48:24 6 Q And what is the date of that document?

10:48:26 7 A The date of that document is May 9th, 2008.

10:48:27 8 Q If we could turn to page 7.

10:48:35 9 Do you recognize the document that begins on page 7?

10:48:38 10 A Yes, I do.

10:48:38 11 Q What is the document that begins on page 7?

10:48:41 12 A So this is a communication from a project manager at  
10:48:47 13 FDA's DMEP sharing the minutes from the pre-IND meeting with  
10:48:55 14 the agent acting on behalf of Amarin.

10:48:59 15 Q And if we could turn now to page 24.

10:49:05 16 And do you recognize the document that begins on  
10:49:15 17 page 24?

10:49:15 18 A Yes, I do.

10:49:16 19 Q What is this document?

10:49:18 20 A This is a communication from that same project manager at  
10:49:24 21 FDA's DMEP again to the agent acting on behalf of Amarin.  
10:49:32 22 It's dated May 20th of 2008, and it's communicating that  
10:49:37 23 FDA -- they're acknowledging the receipt of that May 9th  
10:49:44 24 pre-IND meeting request, and they're assigning to Amarin a  
10:49:49 25 specific pre-IND number.

1 Q If we could turn to page 27.

2 What is the document that begins at page 27?

3 A This is -- appears to be a communication from that same  
4 project manager at FDA's DMEP, and it's attaching a copy of  
5 the official meeting minutes from that pre-IND interaction.

6 Q Okay. And if we turn to page 28.

7 What is the document that begins on page 28?

8 A So on page 28 is the beginning of a correspondence from  
9 that same project manager at FDA's DMEP to the agent of  
10 Amarin, thi is on May 22nd, 2008, and it's basically  
11 communicating that the sponsor's request for a meeting has  
12 been granted and that the meeting will be held on July 14,  
13 2008, at the FDA campus, and it identifies the tentatively  
14 identified individuals from FDA who would participate in that  
15 interaction.

16 Q Okay. And if you could turn to page 31 of the  
17 document -- I'm sorry, 31 of Plaintiff's Exhibit 482.

18 And what is the document that begins on page 31?

19 A It's a communication from the director of the FDA's DMEP  
20 to Amarin's agent, and it is -- apparently there had been a  
21 request from Amarin, specific date, requesting revision of  
22 those official meeting minutes of the pre-IND meeting, and  
23 it's communicating FDA's feedback to those various requests  
24 from Amarin.

25 MS. KEANE: Okay. And, Your Honor, plaintiffs

10:52:05 1 move to admit Plaintiff's Exhibit 482 with the caveat that I  
10:52:09 2 mentioned earlier about requesting time to seal the document.

10:52:12 3 MR. KLEIN: No objection.

10:52:14 4 THE COURT: Exhibit 482 is admitted.

10:52:14 5 (Plaintiff's Exhibit 482 received in  
10:52:14 6 evidence.)

10:52:14 6 BY MS. KEANE:

10:52:18 7 Q So, Dr. Ketchum, if we could turn back to the timeline.

10:52:22 8 You referenced a pre-IND meeting that occurred in  
10:52:26 9 the contents of the document. When did that meeting occur?

10:52:30 10 A It occurred on July 14th of 2008.

10:52:33 11 Q Okay. And are the discussions at that meeting reflected  
10:52:37 12 in the document that begins on page 8 of Exhibit 482?

10:52:42 13 A (Witness reviews document.)

10:52:51 14 Yes. They begin on that page 8.

10:52:54 15 Q And do the meeting minutes reflect who attended the  
10:52:58 16 meeting on behalf of Amarin?

10:52:59 17 A Yes. It towards the bottom of page 8 under the External  
10:53:04 18 Constituent Attendees.

10:53:07 19 MS. KEANE: And, Mr. Brooks, if we could pull up  
10:53:09 20 the attendees.

10:53:09 21 BY MS. KEANE:

10:53:11 22 Q And, Dr. Ketchum, who attend the meeting on behalf of  
10:53:14 23 Amarin?

10:53:14 24 A Dr. Declan Doogan, who is the head of research and  
10:53:19 25 development, Dr. Mehar Manku, vice-president of research,

10:53:25 1 Chris Shilling, who is project management consultant to  
10:53:28 2 Amarin, Dr. Pierre Wicker, a clinical strategy consultant to  
10:53:32 3 Amarin, Adam Woolley, who is a nonclinical strategy  
10:53:36 4 consultant, and David Zuchero who is a regulatory affairs  
10:53:42 5 consultant to Amarin.

10:53:42 6 Q And after --

10:53:45 7 MS. KEANE: Mr. Brooks, we can take down that  
10:53:47 8 exhibit.

10:53:47 9 BY MS. KEANE:

10:53:48 10 Q After the pre-IND meeting in 2008, what happened next  
10:53:51 11 with respect to Amarin's clinical development program?

10:53:55 12 A So Amarin assimilated the feedback that it received at  
10:53:59 13 the pre-IND meeting. There was some aspects that Amarin  
10:54:08 14 needed to address in progressing towards opening.

10:54:12 15 So it had been given in the series of communications  
10:54:16 16 a pre-IND number, and then moved towards opening up an  
10:54:20 17 investigational new drug application, and starting to progress  
10:54:25 18 additional interactions with the Food and Drug Administration  
10:54:28 19 prior to embarking on its clinical development program.

10:54:32 20 Q And when did the clinical development program actually  
10:54:36 21 start?

10:54:36 22 A It started in -- approximately in 2009. So there was  
10:54:43 23 some other steps and interactions needed with FDA before they  
10:54:47 24 could begin those clinical trials.

10:54:49 25 Q And with which study did the clinical development program

10:54:53 1 start?

10:54:53 2 A With what we refer to as the MARINE trial.

10:54:57 3 Q When did the MARINE study start?

10:54:58 4 A It started in 2009.

10:55:01 5 Q And when was it concluded?

10:55:04 6 A It was concluded in late -- towards the very end of 2010.

10:55:10 7 Q And what was the purpose -- what was the purpose of the  
10:55:14 8 MARINE study?

10:55:15 9 A Of the MARINE study?

10:55:17 10 Q Yes.

10:55:17 11 A Yes. So the purpose was to fulfill that unmet medical  
10:55:23 12 need that I spoke to earlier.

10:55:24 13 It was to demonstrate that robust triglyceride  
10:55:29 14 reductions could be achieved in severely hypertriglyceridemic  
10:55:35 15 patients but with a tolerability and safety profile that  
10:55:39 16 helped to differentiate it from some of the existing products.

10:55:42 17 Q And what are the existing products that you're referring  
10:55:45 18 to?

10:55:45 19 A So at this point in time there were a number of products  
10:55:50 20 that had triglyceride-lowering effects and that were approved  
10:55:54 21 in this space.

10:55:55 22 They included Lovaza, which was the omega-3 acid  
10:56:01 23 ethyl esters product I mentioned, and then there were multiple  
10:56:05 24 Fenofibrate containing products, and also multiple niacin  
10:56:10 25 containing products.

Q And do these products that were available, do they have any side effects associated with them?

A All drugs have side effects. But, yes, each of those have their own particular safety and tolerability profile.

In the case of Lovaza, the pivotal trials that are reflected in that approved label had shown that it did reduce triglycerides, but that those reductions were associated with an increase in bad cholesterol, and there were also certain gastrointestinal tolerability profile that was described within the label.

In terms of fibrates, they can also be associated with increases in bad cholesterol, and they can also be associated with other side effects such as muscle pain, particularly in combination with statin therapy.

And then niacin containing products, I'd say the most significant reaction can be a flushing, a facial reddening that can lead both the physician or patient to withdraw from that therapy in this window of time that we're talking about.

And so the goal was to have the product that differentiated itself from those other existing therapies.

Q Are there documents that describe the design of the MARINE study?

A Yes. The clinical study report describes the design of the MARINE study.



10:57:55 1 Q And if we could turn to Exhibit 807 in your binder.

10:57:59 2 MS. KEANE: And I'll also note, Your Honor, for  
10:58:01 3 the record that Exhibit 807 is on the parties' list of  
10:58:05 4 admitted exhibits.

10:58:06 5 THE COURT: Thank you.

10:58:07 6 BY MS. KEANE:

10:58:11 7 Q And, Dr. Ketchum, do you recognize Exhibit 807?

10:58:14 8 A Yes, I do.

10:58:15 9 Q And what is Exhibit 807?

10:58:19 10 A This is the final clinical study report for the MARINE  
10:58:23 11 trial.

10:58:24 12 Q And who prepared the MARINE clinical study report?

10:58:32 13 A So the study report was prepared by the individuals who  
10:58:37 14 are delineated on the next page, on page 2 of the clinical  
10:58:43 15 study report.

10:58:44 16 Q And just a further explanation, what is a clinical study  
10:58:50 17 report?

10:58:50 18 A So a clinical study report is a detailed description of a  
10:58:55 19 clinical study design. Its objectives, the -- both primary,  
10:59:04 20 secondary, tertiary objectives. It lists out in considerable  
10:59:10 21 detail the endpoints including the primary endpoint of focus  
10:59:15 22 and any secondary, tertiary, exploratory endpoints.

10:59:18 23 It spells out how the study is going to be  
10:59:24 24 conducted. So inclusion-exclusion criteria, the various  
10:59:29 25 visits that the patients are going to be required to follow

10:59:33 1 consistent with the study design.

10:59:35 2 And then it also reports out all of the results  
10:59:39 3 across those various efficacy and safety variables.

10:59:43 4 Q And was the MARINE clinical study report submitted to  
10:59:47 5 FDA?

10:59:48 6 A Yes, it was submitted to FDA as part of the original new  
10:59:52 7 drug application.

10:59:54 8 MS. KEANE: And, Mr. Brooks, if we could go to  
10:59:56 9 page 27, Figure 1.

10:59:56 10 BY MS. KEANE:

11:00:02 11 Q And, Dr. Ketchum, could you explain what Figure 1 on  
11:00:06 12 page 27 shows.

11:00:06 13 A So Figure 1 on that page 27 is showing at eye level the  
11:00:12 14 design of the MARINE study.

11:00:14 15 Q Could you briefly walk us through what the design of the  
11:00:17 16 MARINE study was?

11:00:19 17 A Yes, so the MARINE study involved a 4- to 6-week lead in  
11:00:24 18 period. The purpose of that period, other lipid altering  
11:00:30 19 drugs beyond statins and an agent known as ezetimibe, any  
11:00:36 20 agent beyond those two were not allowed in the study, so if  
11:00:40 21 patients were on those they needed to be washed out.

11:00:44 22 And the other purpose was they were intended to be  
11:00:47 23 on a stable diet and exercise regimen.

11:00:52 24 And then there was a 2- to 3-week qualifying period  
11:00:56 25 across these various phases, samples, blood is being taken

1 periodically ultimately to determine if they meet the  
2 inclusion criterion of the triglyceride levels for example.

3 If they met the study inclusion and inclusion  
4 criteria, that larger area shows that they could meet the  
5 criteria and be randomized or enrolled into the study in a  
6 one-to-one-to-one manner, that means a third, a third, and a  
7 third of the patients were enrolled on to either the placebo  
8 arm, the Vascepa 2-gram per day arm, or the Vascepa 4-gram per  
9 day arm, and then they were followed across the pivotal  
10 12-week safety and efficacy safety period with the primary  
11 endpoint being determined at the end of that 12-week period.

12 And then in MARINE patients could also be enrolled  
13 at a dose of 4 grams per day into a 40-week open label  
14 extension phase.

15 MS. KEANE: If we could -- Mr. Brooks, if we  
16 could turn to section 9.1.1 as refers to the screening period.

17 BY MS. KEANE:

18 Q What was the -- what was the screening period that's  
19 referred to here?

20 A So the screening period was a 4- or 6-week diet and  
21 lifestyle stabilization period and wash out period as I  
22 mentioned.

23 Q What was the purpose of the diet and lifestyle  
24 stabilization period?

25 A Again, these patients, these severely

1 hypertriglyceridemic patients have a chronic asymptomatic  
2 condition. They have excessive levels of fat in their blood.

3 So the classic way to approach these patients is to  
4 also ensure that their intake of dietary fat is not excessive  
5 and is healthy because you certainly don't want to contribute  
6 to the underlying condition in that manner.

7 As I mentioned, triglycerides, those fats in your  
8 blood, they do serve a purpose if they're at controllable  
9 levels, and that is that your body deploys them to parts of  
10 your body to be used as energy storage.

11 So they're stored in your fat cells, and then, as an  
12 example in between meals or in periods of exercise, they can  
13 be deployed to be used for energy.

14 So that's a long way of saying that you needed to  
15 control the intake so that you weren't contributing to adding  
16 even more fat to the blood, and that people were not  
17 sedentary, that they were having some level of physical  
18 activity that they would continue throughout the trial, and  
19 that takes a period of time for people to become, let's say,  
20 customary to.

21 Q And what was the purpose of the wash-out period?

22 A So the focal point of this study was on the ability of  
23 Vascepa to lead to robust triglyceride reductions. So the  
24 purpose of the wash-out -- so washing out of other lipid  
25 altering medications was to reduce a potentially confounding

1 variable of having other agents onboard that could potentially  
2 in the backdrop be also contributing to, you know, some aspect  
3 of lipid reduction.

4 MS. KEANE: And, Mr. Brooks, if we could go back  
5 to Figure 1.

6 BY MS. KEANE:

7 Q So you just -- you mentioned the 40-week open label  
8 extension previously. What was the purpose of the 40-week  
9 open label extension?

10 A Right. So in the discussions with FDA, Amarin was laying  
11 out its plans for its development program, and, you know, this  
12 is a drug that's being developed as a new chemical entity for  
13 a chronic condition, and there are standard international kind  
14 of regulatory considerations for how to design a development  
15 program and the expected requirements across all the major  
16 regions, including the United States.

17 And that -- to kind of simplify that, what they're  
18 looking for is a certain minimum number of patients who are  
19 exposed to the drug in question for a -- and a certain minimum  
20 number of patients who are exposed to the study drug across a  
21 one year or longer period of time.

22 So the purpose of that 40-week open label extension  
23 was to contribute to meeting that internationally recognized  
24 and FDA agreed requirement to have a number certain number of  
25 patients exposed to the 4-gram per day dose of Vascepa for a

11:06:01 1 year, so the 12-week, plus the 40-week, meeting that one year  
11:06:05 2 level of exposure.

11:06:06 3 Q An what is the purpose of the 12-week safety and efficacy  
11:06:11 4 portion of the MARINE trial?

11:06:13 5 A So that portion was what we would call the pivotal  
11:06:17 6 portion of the trial in that it was, unlike that 40-week  
11:06:23 7 extension which was open label, the 12-week portion was a  
11:06:28 8 double-blind, placebo-controlled. So that was -- the pivotal  
11:06:35 9 determination of safety and effectiveness was done in that  
11:06:40 10 12-week window.

11:06:41 11 Q And if we take a look at Figure 1, it refers to both  
11:06:48 12 ARM1014 grams per day and AMR 1012 grams per day. Did Amarin  
11:06:54 13 evaluate two different dosage strengths during the MARINE  
11:06:59 14 study?

11:06:59 15 A Yes, Amarin evaluated those two doses.

11:07:04 16 Q And why did Amarin evaluate both a 2-gram and a 4-gram  
11:07:09 17 dose of ARM101?

11:07:13 18 MR. KLEIN: Objection, Your Honor. These  
11:07:14 19 documents are -- the witness doesn't have personal knowledge  
11:07:16 20 of the documents.

11:07:18 21 I'm giving counsel some leeway to walk through  
11:07:20 22 the documents to tell the story, but to the extent questions  
11:07:24 23 are being asked about documents before the witness was there,  
11:07:26 24 I object.

11:07:28 25 MS. KEANE: I mean, Your Honor, I think we've

1 established that Dr. Ketchum certainly has foundation with  
2 respect to various different documents that we are talking  
3 about.

4 He -- one of his responsibilities at Amarin is  
5 to be familiar with the regulatory history as well as the  
6 clinical development program, and that would include the  
7 design and the conduct of the studies that are -- support the  
8 ultimate approval of the product.

9 THE COURT: I assume that because you asked he's  
10 going to know the answer. What would be the source of  
11 information that provides the answer? His review of the  
12 documents?

13 MS. KEANE: I believe it would be a combination  
14 of his review of the documents and his interaction over time  
15 with obviously other individuals at the company, and having to  
16 understand that full development history for purposes of his  
17 employment.

18 MR. KLEIN: Then I'll add hearsay to the  
19 objection.

20 THE COURT: Ultimately the issue isn't that  
21 significant, is it, why the 2 grams a day was included, is it?

22 Mr. KLEIN: No, and that's why generally I've  
23 been giving a lot of leeway on this, and I will be asking some  
24 questions because the witness was 30(b)(6) witness. But I  
25 think comments that go beyond the scope of the documents

1 should be limited before he was at -- before he joined the  
2 company.

3 THE COURT: Well, this is a bench trial, and I  
4 certainly -- I think that the evidentiary issues are more  
5 relaxed. I'll allow the question to be asked, and I'll give  
6 the answer whatever weight I think it should be given.

7 I have another question out of curiosity. I  
8 know this is not relevant.

9 If the study was designed with the four- to  
10 six-week lead-in period where the subjects in the clinical  
11 trial were expected to regulate their diet and exercise, how  
12 can Amarin isolate the reason for the reduction in TG to the  
13 omega -- to EPA versus lifestyle change?

14 I don't know if this witness knows the answer.  
15 I'm just curious.

16 MS. KEANE: And to be clear, is the question for  
17 me or is the question for the witness?

18 THE COURT: Question for you, if you want to  
19 incorporate it, that's great. But if at some point in time  
20 the witness can answer that curiosity question, I would  
21 appreciate it.

22 And while I'm on curiosity, I'm also curious as  
23 to why Vascepa developed the .5-milligram capsule when the  
24 recommended dosage is 4 grams. Is it 4 grams or 4 milligrams?  
25 I can't remember. 4 grams?



11:10:08 1 MS. KEANE: It's 4 grams, Your Honor.

11:10:09 2 BY MS. KEANE:

11:10:10 3 Q Dr. Ketchum, maybe now would be a good time to address  
11:10:14 4 Your Honor's question, or Judge Du's question with respect to  
11:10:17 5 the 500-milligram capsules.

11:10:21 6 A Yes. So it was presented as an alternative dosage form.  
11:10:27 7 So one-gram soft-gelatin capsules, there's a certain  
11:10:33 8 proportion of patients who prefer a smaller dosage form.

11:10:38 9 Although there were no challenges encountered during  
11:10:43 10 the clinical trial with the population swallowing the capsule,  
11:10:47 11 there are still some patients who prefer a smaller dosage  
11:10:51 12 form. So we developed that later on. It was actually several  
11:10:55 13 years later after, the one-gram dosage form, just as another  
11:11:00 14 option for patients.

11:11:02 15 THE COURT: Thank you. Did you want to proceed  
11:11:07 16 with your question about the 2 grams?

11:11:09 17 MS. KEANE: Yes, Your Honor.

11:11:09 18 BY MS. KEANE:

11:11:10 19 Q And so, Dr. Ketchum, why is it that Amarin looked at both  
11:11:13 20 a 2-gram and 4-gram dose of AMR 101?

11:11:16 21 A Yes. So this was a topic that emanated from the pre-IND  
11:11:22 22 meeting earlier on.

11:11:24 23 So when I came on board Amarin in February 2012, the  
11:11:32 24 application with FDA was under review. So this is something  
11:11:39 25 that I needed to become deeply familiar with as I was

1 interacting with FDA.

2 And it is classic in drug development to study more  
3 than one dose. So -- and preferably a multiple factor dose  
4 range, meaning, you know, double. So, in this case, not just  
5 4-gram but something that was half at much.

6 And the reason for that is that across -- when you  
7 conduct a patient trial, you need to establish that a  
8 particular dose has a certain safety and efficacy profile, and  
9 ideally your characterizing across multiple doses because not  
10 all patients weigh the same, they're not all the same age,  
11 they don't all have some other background characteristics, and  
12 it's important to establish a body of information that  
13 supports a recommended dose in an average presenting patient  
14 who's presenting with that medical condition.

15 So this was actually discussed and agreed with FDA  
16 that a two full dose range should be studied in the pivotal  
17 safety and efficacy program in this trial.

18 MS. KEANE: Dr. Ketchum, if we could turn to --  
19 or, Mr. Brooks, if we could turn to page 61 of Exhibit 807.  
20 If we could pull up Figure 2.

21 BY MS. KEANE:

22 Q Dr. Ketchum, how many patients were enrolled in MARINE?

23 A As reflected in the second oval down, there were a total  
24 of 229 patients randomized or enrolled in the MARINE study.

25 Q If we could turn back to pages 30 and 31 of Exhibit 807.

1 Can you briefly describe the patient population that  
2 Amarin studied in MARINE.

3 A Yes. So this patient population needed to be willing to  
4 adhere to the study schedule, they needed to be men and women  
5 age 18 or older.

6 They needed to be willing to go off of other lipid  
7 altering therapy, apart from statin, with or without this  
8 other agent Ezetimibe, and then, importantly, they needed to  
9 have fasting triglycerides levels greater than or equal to  
10 500 milligrams per deciliter, and less than or equal to  
11 2,000 milligrams per deciliter, and be willing to maintain a  
12 stable diet and physical activity level throughout the study.

13 Q And why did Amarin impose an upper limit of 2,000  
14 milligrams per deciliter?

15 A So as I mentioned before, these patients -- kind of the  
16 backdrop is these patients with excessive fat levels in their  
17 blood are at risk of acute pancreatitis, and so there was  
18 upper limit established to ensure that if there were  
19 triglyceride fluctuations, that they would not exceed a  
20 certain level that would put the patients at undue risk.

21 Q And why was there a diet and lifestyle stabilization  
22 period before patients were randomized in the study?

23 A So the purpose of the diet and lifestyle, as I mentioned  
24 before, so this is a -- the whole context of this development  
25 program was to move towards a proposed indication where it

1 would be used as an adjunct to diet, and also in a situation  
2 where patients were exercising appropriately.

3 So the purpose of the lead-in phase was to  
4 accommodate them to that study requirement of being on a diet  
5 and being willing to maintain physical activity throughout the  
6 study.

7 And, you know, and that if the patients couldn't  
8 adhere to that, or if, by virtue of that, the patients didn't  
9 meet the other study inclusion criterion such as the fasting  
10 triglyceride levels, then they would not have been enrolled  
11 onto this study.

12 Q Were any of the patients in MARINE on additional lipid  
13 altering medications?

14 A Yes, there were approximately 25 percent of the patients  
15 in MARINE who were on -- concomitantly on a statin.

16 Q And why were some patients permitted to remain on statin  
17 during the period?

18 A It was -- as described in that same section, it was an  
19 allowed medication. Those patients needed the statin to  
20 control their levels of bad cholesterol or LDL-C.

21 Q What was the primary endpoint in MARINE?

22 A The primary endpoint in MARINE was the percentage of TG  
23 reduction, triglyceride reduction out at week 12 in the  
24 Vascepa arm relative to the placebo arm.

25 Q Did MARINE -- I'm sorry, were there any other endpoints

11:16:56 1 that were studied in the MARINE study?

11:17:00 2 A Yes, there were a number of secondary and exploratory  
11:17:04 3 efficacy endpoints in the MARINE study.

11:17:07 4 Q And are the efficacy variables for MARINE reflected in  
11:17:10 5 the clinical study report?

11:17:12 6 A Yes, they are.

11:17:13 7 MS. KEANE: Mr. Brooks, if you could pull up  
11:17:16 8 section 9.5.2 on page 42 of Exhibit 807.

11:17:16 9 BY MS. KEANE:

11:17:24 10 Q And, Dr. Ketchum, could you briefly describe what is  
11:17:26 11 depicted on page 42.

11:17:29 12 A On this page is listed the primary efficacy variable in  
11:17:33 13 the first sentence that I mentioned, and then a series of  
11:17:37 14 secondary efficacy variables are listed in the next sentence,  
11:17:42 15 and it moves on to list other exploratory efficacy variables  
11:17:47 16 and endpoints.

11:17:48 17 Q Okay. If we could focus on the secondary efficacy  
11:17:52 18 variable, there's reference there to VLDL-C?

11:17:57 19 A Yes.

11:17:57 20 Q What is VLDL-C?

11:18:00 21 A It stands for very low-density lipoprotein cholesterol.

11:18:03 22 Q And why was VLDL-C studied?

11:18:07 23 A It's a classic lipid parameter that's collected in lipid  
11:18:13 24 panels and -- especially in triglyceride trials. It's -- VLDL  
11:18:21 25 gets involved in shuttling and transporting triglycerides, and

11:18:26 1 so it's a key aspect to study in these types of trials.

11:18:30 2 Q And the secondary efficacy variables there's also a  
11:18:37 3 reference to apo B. What is apo B?

11:18:40 4 A Apo B is an apolipoprotein that is associated with  
11:18:45 5 atherogenic, so particles -- lipid -- lipoprotein particles  
11:18:53 6 that can contribute to atherosclerosis.

11:18:58 7 MS. KEANE: Mr. Brooks, if you could go to the  
11:19:00 8 next section of the document under Exploratory Efficacy.

11:19:00 9 BY MS. KEANE:

11:19:05 10 Q Dr. Ketchum, there's reference here to LDL-C. What is  
11:19:10 11 LDL-C?

11:19:12 12 A LDL-C is low-density lipoprotein cholesterol commonly  
11:19:17 13 referred to as bad cholesterol.

11:19:18 14 Q And why did Amarin study LDL-C?

11:19:21 15 A LDL-C at this point in time in the 2008-2009 time frame  
11:19:27 16 was the single most highly validated lipid marker.

11:19:32 17 By that I mean a series of pharmaceutical companies  
11:19:37 18 had conducted very large clinical development programs to show  
11:19:43 19 that statins were highly effective in lowering bad  
11:19:48 20 cholesterol, and also that that reduction in low cholesterol,  
11:19:55 21 bad cholesterol, was associated with cardiovascular risk  
11:19:59 22 reduction. So -- and, likewise, that increases in bad  
11:20:06 23 cholesterol were associated with increased cardiovascular  
11:20:12 24 risk.

11:20:12 25 So as the most highly validated lipid marker, it was

1 an expected component of a development program like this.

2 Q Generally speaking, what were the results of the MARINE  
3 study?

4 A So at a high level, the MARINE study robustly met its  
5 primary efficacy endpoint and also achieved its secondary  
6 efficacy endpoints and on down in through the exploratory  
7 endpoints, and it established a safe and tolerable profile as  
8 well.

9 Q And where are the results of MARINE reflected?

10 A They're reflected within this clinical study report, and  
11 then -- obviously which formed the basis for the original new  
12 drug application to FDA, and so the results were reflected  
13 into that review and then subsequently into the approved  
14 prescribing information across various sections of the label,  
15 and the results themselves are described in section 14 of that  
16 approved prescribing information.

17 MS. KEANE: If we could turn to Plaintiff's  
18 Exhibit 1186, Mr. Brooks. If we could pull up Exhibit 1186.  
19 If we could turn to section 14.2.

20 BY MS. KEANE:

21 Q Dr. Ketchum, were you involved with the drafting of  
22 Exhibit 1186?

23 A Yes, I was.

24 Q Okay. And, again, this is Amarin's current prescribing  
25 information?

1 A This is Amarin's current prescribing information for  
2 Vascepa.

3 Q So why is a summary of the MARINE clinical trial included  
4 in section 14.2 of labeling?

5 A So this section is intended to describe the trial or  
6 trials that served as the pivotal basis for the determination  
7 of effectiveness and safety.

8 And so, in this case, the MARINE trial results  
9 formed that pivotal basis for the determination of  
10 effectiveness and safety of Vascepa for the MARINE indication,  
11 and so it's to provide information to the reviewers, the  
12 potential prescribing physicians, around the trial that was  
13 conducted to form that pivotal basis.

14 MS. KEANE: And, Mr. Brooks, if we could focus  
15 on the first paragraph on the top of page 11.

16 BY MS. KEANE:

17 Q And, Dr. Ketchum, what is the purpose of the first  
18 paragraph on page 11 -- I'm sorry, the first paragraph in the  
19 Clinical Study section on page 11 which is also the first  
20 paragraph in the clinical study section?

21 A So the purpose of this paragraph is at a high level to  
22 describe the design of the MARINE study, the inclusion, key  
23 inclusion criterion, and then -- that takes up the first two  
24 sentences of that paragraph, and then in the subsequent number  
25 of sentences on through the end of that paragraph it's



1 basically conveying what we call the baseline demographics or  
2 the baseline characteristics of the patients who were enrolled  
3 into the MARINE study.

4 MS. KEANE: And, Mr. Brooks, if we can now focus  
5 on the next paragraph on page 11.

6 BY MS. KEANE:

7 Q So, Dr. Ketchum, the next paragraph refers to major  
8 lipoprotein lipid parameters. Do you see that?

9 A Yes, I see that.

10 Q What does major lipoprotein lipid parameters mean?

11 A So they are the key lipoprotein and lipid parameters that  
12 were studied in the MARINE study in terms of the primary and  
13 secondary and other endpoints.

14 MS. KEANE: Okay. And, Mr. Brooks, if you could  
15 go down to table 2.

16 BY MS. KEANE:

17 Q Dr. Ketchum, what's depicted in table 2?

18 A So table 2 depicts the results from the MARINE study on  
19 those major lipid and lipoprotein parameters.

20 Q And what was the effect of Vascepa 4 grams per day on  
21 triglyceride levels?

22 A So on triglyceride levels in the far right hand column it  
23 reflects that a 33 percent reduction in triglycerides relative  
24 to placebo was achieved at a dose of 4 grams per day.

25 Q And what was the effect of Vascepa 4 grams per day on

11:24:56 1 apo B?

11:24:58 2 A Treatment with Vascepa at 4 grams per day led to a nine  
11:25:02 3 percent reduction relative to placebo.

11:25:07 4 Q And what was the effect of Vascepa 4 grams per day on  
11:25:13 5 LDL-C?

11:25:14 6 A A minus 2 or 2 percent reduction relative to placebo at a  
11:25:18 7 dose of 4 grams per day of Vascepa.

11:25:21 8 Q And if we could continue down below the table on the same  
11:25:44 9 page, there are a couple of statements there, Dr. Ketchum.  
11:25:48 10 Why did Amarin include this paragraph under table 2 in the  
11:25:55 11 Vascepa labeling?

11:25:56 12 A So this information, as I mentioned, is directed to  
11:26:00 13 healthcare professionals so that as they review it, they're  
11:26:06 14 being apprised of key information from that pivotal trial.

11:26:13 15 And it's -- you know, one can either assume that  
11:26:17 16 someone can glean the key information from a table, or  
11:26:20 17 classically, because you don't want to leave things to chance  
11:26:23 18 in the context of a prescribing information, the intent of  
11:26:28 19 those two sentences is to draw the key information from the  
11:26:33 20 table that's presented above, and it's tied to the asterisked  
11:26:39 21 elements in the first sentence.

11:26:41 22 So the first instance -- or the first sentence below  
11:26:45 23 table 2 is tied to the asterisked elements above in table 2,  
11:26:51 24 which in turn are the -- as we previously discussed, the  
11:26:55 25 primary efficacy variable was triglyceride reduction, and two

1 key secondary efficacy variables were VLDL-C and apo B.

2 So it's drawing the healthcare professional's  
3 attention to that key information and explaining that Vascepa  
4 4 grams per day reduced each of those lipid or lipoprotein  
5 parameters from baseline relative to placebo.

6 The intent of the second sentence is, as I  
7 mentioned, LDL-C or bad cholesterol is the most -- continues  
8 to be the most highly validated lipid marker, and so the  
9 intent of that second sentence was again to draw the  
10 healthcare professional's attention to the fact that in terms  
11 of that important lipid parameter, the treatment with Vascepa  
12 at 4 grams per day led to the reduction in TGs that were  
13 observed, but that observation was not associated with  
14 elevations in bad cholesterol relative to placebo.

15 Q Okay. Dr. Ketchum, we previously talked about -- I  
16 believe you testified that there are about 25 percent of  
17 patients in MARINE who were on concomitant statin therapy; is  
18 that right?

19 A Yes, that was listed in the paragraph above the table 2.

20 Q Did Amarin study whether the results of MARINE were  
21 consistent across patients who took statins and people who did  
22 not take a statin?

23 A Yes. This would have been part of the additional  
24 analyses performed on the data set by Amarin.

25 Q And how did the results between those two groups of

11:28:40 1 patients compare?

11:28:41 2 A There were no differences.

11:28:43 3 Q And where is the analysis that Amarin conducted between  
11:28:50 4 those two patient groups, where is that analysis reflected?

11:28:53 5 A It's reflected at the back of the clinical study report  
11:28:57 6 in what's called a set of posttext tables and figures.

11:29:02 7 MS. KEANE: Okay. If we could turn to  
11:29:04 8 Plaintiff's Exhibit 807, and, Mr. Brooks, if you could bring  
11:29:10 9 up page 459, and, Dr. Ketchum, I would like to direct you to  
11:29:15 10 page 459.

11:29:15 11 BY MS. KEANE:

11:29:22 12 Q Dr. Ketchum, can you explain what is depicted in table  
11:29:25 13 14.2.97?

11:29:28 14 A Yes. As listed in the heading there, in the middle  
11:29:33 15 towards the top, it specifies that this is the subgroup who  
11:29:37 16 was on statin therapy. So this is the subset of patients  
11:29:43 17 receiving co-therapy with statin.

11:29:46 18 And then in the table below, in the top line of  
11:29:53 19 the -- it lists the number of subjects who were on statin  
11:29:57 20 therapy across each of the three treatment groups. It shows  
11:30:02 21 there baseline, and then week 12 endpoint levels, and then,  
11:30:09 22 you know, towards the bottom what it's doing is a statistical  
11:30:14 23 comparison as reflected by the p-values, and it shows that  
11:30:19 24 there's no difference in the LDL-C in this -- across these  
11:30:26 25 various Vascepa treatment groups.

11:30:31 1 Q If we could turn to page 460.

11:30:34 2 Would you explain what's depicted in table 14.2.9 on  
11:30:39 3 page 460.

11:30:40 4 A So this is for the larger subgroup who was not currently  
11:30:46 5 also taking a statin therapy, and, similarly, down towards the  
11:30:53 6 bottom in the right-hand portion it's doing a statistical  
11:30:58 7 comparison between the 2-gram daily dose and the 4-gram daily  
11:31:04 8 dose of Vascepa, and the p-values show that there's no  
11:31:07 9 statistical difference between those values for LDL  
11:31:12 10 cholesterol.

11:31:16 11 Q Okay. And how did the results that are depicted in table  
11:31:22 12 14.2.97 compare with the results in table 14.2.98?

11:31:29 13 A They're comparable.

11:31:32 14 Q I think as we've previously talked about the MARINE study  
11:31:39 15 led to an approved indication; is that right?

11:31:42 16 A Yes, that's correct.

11:31:43 17 Q And that's the MARINE indication?

11:31:45 18 A It's the MARINE indication.

11:31:47 19 Q Do you have an understanding of why the Vascepa was  
11:31:54 20 approved?

11:31:55 21 A Yes. Vascepa was approved for that indication because we  
11:32:01 22 had conducted the study under what's called a special protocol  
11:32:05 23 assessment agreement with FDA. So we prediscussed the study  
11:32:10 24 that we were going to conduct and the analyses that we were  
11:32:14 25 going to perform, and one condition of that agreement was that

1 the trial read out, meet its pre-specified primary endpoint,  
2 and, you know, show a safe and effective profile. So that's  
3 one component as to why the product was approved.

4 That's -- and that has to do with the 12-week  
5 randomized, double-blind, placebo-controlled phase that formed  
6 that part of the basis for approval.

7 Amarin also conducted the 40-week open label  
8 extension phase which formed the basis for another requirement  
9 which was having a certain minimum number of patients exposed  
10 for one year at the intended approved dose which was 4 grams  
11 per day.

12 And then there was a third component that formed the  
13 basis of the acceptability of the application for this  
14 approved indication, and that was the total number of patients  
15 exposed to Vascepa, and so --

16 And also included in the new drug application were  
17 the results of this separate lipid trial that we called  
18 ANCHOR, and so the totality of those data sets formed the  
19 basis for the approval of the MARINE indication.

20 Q And are the -- is your understanding of the reasons for  
21 approval based on any documents or reflected in any documents?

22 A Yes. When FDA reviews a new drug application, a variety  
23 of technical disciplines review the application, including,  
24 importantly, the medical reviewer plays a -- plays a lead role  
25 in that determination, so within FDA's medical review that is

publicly available -- becomes publically available at some point.

Q And if we could turn to Plaintiff's Exhibit 289, what is Exhibit 289?

A So Exhibit 289 is the medical review from FDA in conjunction with our original new drug application based on the MARINE study.

MS. KEANE: Mr. Brooks, if you could pull up section 6.1.9 on page 68 as well as the corresponding figure on the next page.

BY MS. KEANE:

Q Dr. Ketchum, can you explain what is depicted in section 6.1.9 of the medical review.

A Yes. So this is a section of the medical review where the medical reviewer is touching on the aspects pertaining to persistence of efficacy.

And so the medical reviewer is -- through its team -- or actually in -- this particular figure actually was sourced from the MARINE clinical study report itself. So the medical review -- medical reviewer would have had access to this figure from the clinical study reports submitted by Amarin.

And what this medical reviewer is drawing attention to is, in that second sentence, where it's talking about the maximum TG-lowering effect, speaking to the lowest curve on

11:36:25 1 that plot, the one that in -- the key further below is showing  
11:36:29 2 the inverted red triangles, those data points pertain to the  
11:36:36 3 Amarin -- the Vascepa, the 4-gram per day dose, and it's  
11:36:39 4 saying that the maximum effects occurred by week four and that  
11:36:43 5 they were maintained throughout the 12-week study.

11:36:47 6 And it's comparing and contrasting that observation  
11:36:52 7 to what was observed in the intermediate curve within that  
11:36:59 8 plot, which is the dashed line with the blue crosses.

11:37:07 9 And it's -- you know, and then the other part of  
11:37:12 10 that same sentence is acknowledging that there were certain TG  
11:37:18 11 fluctuations in the third arm of the study, which was the  
11:37:22 12 highest curve with the solid line and the green diamonds.

11:37:36 13 So the medical reviewer is essentially concluding  
11:37:39 14 that the Vascepa 4-gram per day dose led to maximal effects by  
11:37:47 15 week four and maintaining those effects through the 12-week  
11:37:51 16 study period.

11:37:52 17 Q And, Dr. Ketchum, you explained earlier that there were  
11:37:56 18 additional safety requirements that Amarin was required to  
11:38:00 19 meet in support of its NDA; is that right?

11:38:04 20 A Yes, that's correct.

11:38:05 21 Q And are there -- is the requirement for those -- well,  
11:38:16 22 let me back up.

11:38:17 23 How did Amarin meet FDA's additional safety  
11:38:22 24 requirements?

11:38:23 25 A So it met those requirements through the 40-week open



1 label extension phase of MARINE. So that satisfied the  
2 component of having a certain minimum number of patients  
3 exposed to one year at the dose of 4 grams per day.

4 And then separately Amarin conducted the ANCHOR  
5 12-week study which had an additional 702 patients enrolled,  
6 and that satisfied the requirement for, you know, a multi  
7 hundred number of patients exposed to the study drop in total.

8 Q And FDA ultimately concluded that Vascepa was safe for  
9 the intended use?

10 A Yes, yes, the FDA did.

11 Q Are there any documents that reference or reflect FDA's  
12 safety requirements for Vascepa?

13 A Yes. So within the same medical review, obviously teams  
14 of medical reviewers review different drugs across  
15 different -- from different sponsors, and there's a checklist  
16 that -- a guidance, basically that they're given for their  
17 review, and that appears at the end of the -- that checklist  
18 appears at the end of the medical review.

19 MS. KEANE: Mr. Brooks, if we could pull up  
20 page 138 of Exhibit 289.

21 BY MS. KEANE:

22 Q And, Dr. Ketchum, is the checklist that you're referring  
23 to, is that where it's reflected on page 138?

24 A Yes, that's the start of the clinical checklist.

25 Q And what is the purpose of the clinical filing checklist?

11:40:17 1 A So it's intended to -- it follows a defined format and  
11:40:24 2 lists the domains that the medical reviewer or the clinical  
11:40:28 3 review team is expected to touch upon during its review to  
11:40:33 4 ensure that there's a thorough review for all of the expected  
11:40:37 5 components that would support a recommendation for approval as  
11:40:43 6 a safe and effective drug for that proposed indication.

11:40:47 7 Q Where are the safety requirements reflected in the  
11:40:50 8 checklist?

11:40:50 9 A There's a separate -- that checklist is separated by  
11:40:55 10 subheadings involved and there is a safety related subsection.

11:41:04 11 MS. KEANE: Mr. Brooks, if you could pull up  
11:41:08 12 page 142, and if we could focus on the safety section.

11:41:08 13 BY MS. KEANE:

11:41:21 14 Q Dr. Ketchum, could you explain what's depicted here in  
11:41:25 15 the safety section of the NDA filing checklist.

11:41:28 16 A Yes. So it's again spelling out certain content aspects  
11:41:36 17 from a new drug application that are phrased as questions to  
11:41:40 18 the medical reviewer for them to answer yes, no, or not  
11:41:44 19 applicable, and what I was speaking to was element 21.

11:41:55 20 So severe hypertriglyceridemia, again, it's a  
11:42:01 21 chronic asymptomatic condition. This was a new chemical  
11:42:05 22 entity being submitted so it's expected to abide by ICH or --  
11:42:10 23 that's an abbreviation for the International Conference on  
11:42:13 24 Harmonization.

11:42:15 25 So the major regions of Japan, Europe, and the U.S.

1 came together over a series of years and spelled out certain  
2 guidelines across certain topics including in this instance  
3 safety, and so they had certain expectations about the  
4 exposure information that a sponsor is going to provide in a  
5 new drug application.

6 And in this instance, the medical reviewer ticked  
7 yes in that box. And there's a footnote 1 that provides some  
8 additional information and it's -- again, this is a  
9 recommendation.

10 It gives the medical reviewer and FDA some latitude  
11 depending on the drug in question. The patient population in  
12 question are not absolutely rigid. But they are expected to  
13 approach or meet these types of numbers for chronically  
14 administered drugs.

15 And that's where the 100 patients for one year  
16 aspect was met by the randomized, double-blind,  
17 placebo-controlled portion of the MARINE study, plus the  
18 40-week open label component, and that open label component  
19 was conducted at 4 grams per day which factors into the  
20 whole -- the last sentence about the dose or dose range  
21 believed to be efficacious.

22 And then the 229 patients in the MARINE study, plus  
23 the 702 patients enrolled in ANCHOR approached a thousand  
24 patients so -- and in the context of arguably a safer than  
25 average drug class, all of these factors led to the medical

reviewer ticking that box yes.

MS. KEANE: If we could -- Mr. Brooks, if we could focus on line 22, or row 22.

BY MS. KEANE:

Q And, Dr. Ketchum, what does row 22 convey?

A So row 22 is highlighting another potential scenario that might face the medical reviewer in the context of a submitted new drug application.

Some drugs are not intended for chronic administration, they're intended for intermittent or short course use, and in that situation then the medical reviewer is being asked, you know, have the requisite number of patients been exposed, and the medical reviewer has ticked this not applicable because of his or her answer to 21.

MS. KEANE: Dr. Ketchum -- or, Mr. Brooks, we can take down this exhibit.

BY MS. KEANE:

Q Did Amarin submit data from any preclinical studies as part of its NDA for the MARINE indications?

A Yes. As discussed in the pre-IND meeting in July 2008, because this was a new chemical entity for a chronic disease state, Amarin was required to conduct what's called carcinogenicity studies. So essentially these are studies of the ability of a drug to contribute to uncontrolled cell growth or cancer.

11:45:39 1 It's an important component particularly for new  
11:45:42 2 chemical entities and chronically administered drugs, and we  
11:45:46 3 were required to conduct those studies in two species and fold  
11:45:51 4 that information into our new drug application.

11:45:54 5 Q And is the requirement -- was that preclinical  
11:45:57 6 requirement reflected in any documents?

11:46:01 7 A Yes. So it was -- after being discussed at the pre-IND  
11:46:07 8 meeting, it ultimately -- after we had conducted the studies  
11:46:10 9 and submitted the information, it's folded into the approved  
11:46:14 10 prescribing information for Vascepa.

11:46:19 11 MS. KEANE: And, Mr. Brooks, if we could pull up  
11:46:21 12 page 7 of Exhibit 482. Exhibit 482 is previously admitted.

11:46:21 13 BY MS. KEANE:

11:46:30 14 Q Dr. Ketchum, for the record, what is the document that  
11:46:32 15 begins on page 7 of Exhibit 482?

11:46:35 16 A So this is the cover page from the FDA project manager at  
11:46:49 17 DMEP sharing the official minutes of that pre-IND meeting with  
11:46:53 18 Amarin.

11:46:53 19 Q And where in the document is the requirement for  
11:46:57 20 preclinical studies discussed?

11:47:02 21 A So in preparing its request for the meeting, Amarin posed  
11:47:06 22 a series of questions arranged by topics according to the  
11:47:11 23 technical discipline, and there's a nonclinical -- a series of  
11:47:16 24 nonclinical questions within those meeting minutes that  
11:47:19 25 contain Amarin's question and FDA's response, and that

1 appears -- I believe it's question -- nonclinical question  
2 number six.

3 MS. KEANE: Mr. Brooks, if we could pull up  
4 question six starting on page 11.

5 BY MS. KEANE:

6 Q And, Dr. Ketchum, what is reflected in question number  
7 six on page 11?

8 A So the italicized text at the top is Amarin's question to  
9 FDA, and it's essentially proposing not to need to further  
10 study the carcinogenic potential of the icosapent ethyl.

11 The bolded preliminary response is from FDA and was  
12 communicated to Amarin in advance of the face-to-face meeting.  
13 The preliminary response was no.

14 It's generally expected that a carcinogenicity study  
15 be conducted in two rodent species to support marketing  
16 approval of a new chemical entity for a chronic use  
17 indication, and essentially leading up to the meeting  
18 discussion, which we affirmed the need for Amarin -- that's  
19 the subsequent underlined text beginning at the bottom of that  
20 screen, and at the end, Amarin needed to perform those two  
21 carcinogenicity studies in each of two rodent species.

22 Q In the section titled Preliminary Response there's  
23 reference to chronic use indication. Do you see that?

24 A Yes.

25 Q What chronic use indication is that referring to?

11:49:11 1 A That's referring to the MARINE indication.

11:49:14 2 Q There's also a reference in that section to a new  
11:49:19 3 chemical entity. Do you see that?

11:49:21 4 A Yes.

11:49:21 5 Q What is a new chemical entity?

11:49:24 6 A A new chemical entity is a -- basically, a chemical  
11:49:32 7 compound that has never been approved before, and so it's --  
11:49:40 8 it doesn't exist in nature as it is, and has never before been  
11:49:49 9 progressed through a clinical development program and moved  
11:49:54 10 towards an approved pharmaceutical use.

11:49:56 11 Q And the carcinogenicity studies that are referenced in  
11:50:06 12 question number six, did Amarin perform those carcinogenicity  
11:50:12 13 studies?

11:50:12 14 A Yes, Amarin did.

11:50:14 15 Q And where are the results of those studies reflected?

11:50:16 16 A They're reflected in the approved prescribing information  
11:50:20 17 for Vascepa.

11:50:20 18 Q If we could turn back to Plaintiffs' Exhibit 1186. Where  
11:50:27 19 are those results reflected in Exhibit 1186?

11:50:32 20 A So the nonclinical section of the label is section 13.

11:50:39 21 MS. KEANE: And, Mr. Brooks, if we could pull up  
11:50:42 22 section 13.

11:50:42 23 BY MS. KEANE:

11:50:48 24 Q And where specifically in section 13 are the  
11:50:52 25 carcinogenicity studies reflected?

11:50:55 1 A So the rat study appears in the first paragraph of  
11:51:00 2 section 13.1, and the mouse study appears in paragraph 2 of  
11:51:06 3 section 13.1.

11:51:07 4 Q And generally speaking, what were the results of the  
11:51:10 5 carcinogenicity studies?

11:51:12 6 A Neither -- so both studies supported there was no  
11:51:16 7 carcinogenic potential of icosapent ethyl.

11:51:30 8 Q Dr. Ketchum, I want to change gears a little bit.

11:51:34 9 How did the MARINE study support Amarin's ability to  
11:51:40 10 differentiate Vascepa from other triglyceride-lowering  
11:51:42 11 medications?

11:51:44 12 A So as I mentioned before, the other existing therapies  
11:51:52 13 were associated with increases in LDL-C or bad cholesterol.  
11:51:57 14 Our MARINE study showed that the triglyceride reductions were  
11:52:00 15 not associated with those rises in bad cholesterol so that was  
11:52:04 16 one point of differentiation.

11:52:07 17 And then another was within the adverse effects  
11:52:11 18 section. We -- our product was shown not to be associated  
11:52:16 19 with some of the side effects that are reported in the labels  
11:52:21 20 of those other products.

11:52:23 21 Q Okay. And does Amarin promote Vascepa as a treatment for  
11:52:26 22 reducing triglycerides in adult patients with severe  
11:52:30 23 hypertriglyceridemia?

11:52:31 24 A Yes, Amarin does.

11:52:32 25 Q And does Amarin mention Vascepa's lack of an effect on



11:52:36 1 LDL-C when promoting Vascepa?

11:52:40 2 A Yes, Amarin does.

11:52:41 3 MS. KEANE: Mr. Brooks, can we pull up  
11:52:44 4 Exhibit 287.

11:52:44 5 BY MS. KEANE:

11:52:46 6 Q And, Dr. Ketchum, if could you take a look at  
11:52:49 7 Exhibit 287. What is Exhibit 287?

11:52:52 8 A Exhibit 287 is a direct-to-consumer print advertisement  
11:53:00 9 for Vascepa.

11:53:00 10 Q And are you familiar with Exhibit 287?

11:53:03 11 A Yes, I am.

11:53:09 12 MS. KEANE: Your Honor, plaintiffs move to admit  
11:53:11 13 Exhibit Plaintiffs' 287 into evidence.

11:53:14 14 MR. KLEIN: No objection.

11:53:14 15 THE COURT: Exhibit 287 is admitted.

11:53:14 16 (Plaintiff's Exhibit 287 received in  
11:53:17 evidence.)

11:53:17 17 BY MS. KEANE:

11:53:18 18 Q Dr. Ketchum, does Plaintiffs' Exhibit 287 make any  
11:53:21 19 reference to LDL-C?

11:53:23 20 A Yes, it does. In the right middle portion that's  
11:53:30 21 demarcated by two lines there in the second paragraph, it says  
11:53:38 22 that Vascepa, along with diet, is clinically proven to lower  
11:53:43 23 very high triglycerides by 33 percent in adults without  
11:53:47 24 raising bad cholesterol, and then there's a qualifying  
11:53:52 25 footnote.

11:53:54 1 Q If you could turn to Plaintiffs' Exhibit 286 in your  
11:53:59 2 binder as well.

11:54:02 3 MS. KEANE: And, Mr. Brooks, could you pull up  
11:54:04 4 Exhibit 286.

11:54:04 5 BY MS. KEANE:

11:54:06 6 Q What is Exhibit 286?

11:54:09 7 A So as indicated at the top, this is a direct-to-consumer  
11:54:18 8 TV ad for Vascepa, and this is what's called a storyboard. So  
11:54:23 9 it lays out the flow of the TV ad.

11:54:29 10 Q And, Dr. Ketchum, are you familiar with Plaintiffs'  
11:54:33 11 Exhibit 286?

11:54:33 12 A Yes, I am.

11:54:34 13 MS. KEANE: Your Honor, plaintiffs move to admit  
11:54:36 14 Plaintiffs' Exhibit 286 into evidence.

11:54:38 15 MR. KLEIN: No objection.

11:54:38 16 THE COURT: 286 is admitted as well.

11:54:38 17 (Plaintiffs' Exhibit 286 received in  
11:54:43 evidence.)

11:54:43 18 BY MS. KEANE:

11:54:43 19 Q Dr. Ketchum, does Plaintiffs' Exhibit 286 make any  
11:54:46 20 reference to LDL-C?

11:54:49 21 A Yes, it does. It's in frame 11, or storyboard 11, on  
11:54:58 22 page 3 of that exhibit.

11:55:00 23 MS. KEANE: And, Mr. Brooks, if we could turn to  
11:55:02 24 page 3 and pull up slide 11.

11:55:11 25 THE WITNESS: So in that frame it's conveying --

11:55:14 1 and there's a voiceover, the acronym AVO is speaking to an  
11:55:19 2 audio voice over which, in conjunction with the visual there  
11:55:24 3 in the center of that screen, is saying that Vascepa along  
11:55:27 4 with diet is clinically proven to lower very high  
11:55:32 5 triglycerides by 33 percent of adults without raising bad  
11:55:36 6 cholesterol.

11:55:36 7 BY MS. KEANE:

11:55:37 8 Q And does Amarin believe it's permissible to reference  
11:55:40 9 Vascepa's effect on LDL-C in its promotional materials?

11:55:46 10 A Yes.

11:55:47 11 Q And why is that?

11:55:49 12 A That's because it's a part of the approved prescribing  
11:55:52 13 information for Vascepa.

11:55:53 14 Q And does FDA regulate prescription drug promotion?

11:55:58 15 A Yes, it does.

11:55:58 16 Q And has Amarin asked FDA to review its promotional  
11:56:04 17 materials?

11:56:04 18 A Yes. These DTC print advertisement and TV spot  
11:56:10 19 storyboard were shared with FDA's Office of Prescription Drug  
11:56:15 20 Promotion for their review in advance of finalization and  
11:56:20 21 dissemination.

11:56:21 22 Q And has FDA -- to your knowledge, has FDA raised a  
11:56:25 23 concern with Amarin regarding Vascepa promotional materials  
11:56:29 24 that reference the lack of LDL-C increase?

11:56:33 25 A No.

11:56:33 1 Q Could we take a look at Exhibit 762, and, Dr. Ketchum,  
11:56:46 2 what is Plaintiffs' Exhibit 762?

11:56:49 3 A Exhibit 762 is a letter from FDA's Office of Prescription  
11:56:58 4 Drug Promotion from the NSPO regulatory review officer at OPDP  
11:57:06 5 addressed to me conveying their feedback in response to a  
11:57:11 6 submission that we made containing a draft print DTC  
11:57:16 7 advertisement and a draft TV ad storyboard.

11:57:20 8 Q And what are those draft print advertisements and DTC  
11:57:25 9 storyboards?

11:57:25 10 A They were in the prior materials that we just pulled up  
11:57:30 11 onto the screen.

11:57:30 12 Q They were Plaintiffs' Exhibits 286 and 287?

11:57:33 13 A Yes.

11:57:38 14 Q And Plaintiffs' Exhibit 762, that's addressed to you?

11:57:40 15 A Yes, it is.

11:57:42 16 Q And are you familiar with this document?

11:57:46 17 A I am.

11:57:46 18 MS. KEANE: Your Honor, plaintiffs also move to  
11:57:48 19 admit Plaintiffs' Exhibit 762 into evidence.

11:57:52 20 MR. KLEIN: No objection.

11:57:52 21 THE COURT: 762 is admitted.

11:57:52 22 (Plaintiffs' Exhibit 762 received in  
11:57:55 evidence.)

11:57:55 23 BY MS. KEANE:

11:57:55 24 Q And, Dr. Ketchum, can you explain what role Exhibit 762  
11:57:59 25 played in FDA's review process.

11:58:04 1 A So Exhibit 762 was the end, the culmination of their  
11:58:11 2 review of our proposed DTC promotional materials.

11:58:16 3 Q And what concerns, if any, did FDA raise regarding the  
11:58:19 4 statements -- the statements regarding Vascepa's effect on  
11:58:24 5 LDL-C?

11:58:25 6 A FDA had no requested or proposed revisions to those  
11:58:31 7 statements.

11:58:33 8 Q Okay. Dr. Ketchum, I would like to turn to the ANCHOR  
11:58:42 9 study, and this is the second study that you referenced  
11:58:47 10 earlier in your testimony with respect to Vascepa. What was  
11:58:50 11 the ANCHOR study designed to evaluate?

11:58:54 12 A So the ANCHOR study was in a different  
11:59:03 13 hypertriglyceridemic patient population. So the goal of this  
11:59:06 14 study, these were patients to contrast with the severely  
11:59:10 15 hypertriglyceridemic patients, these were patients that had  
11:59:13 16 multiple lipid abnormalities.

11:59:17 17 So their primary lipid abnormality was they needed  
11:59:23 18 statin to control their bad cholesterol, and in spite of that,  
11:59:27 19 they had elevated triglycerides in the range of 200 to  
11:59:31 20 499 milligrams per deciliter.

11:59:34 21 So the goal of this study was to demonstrate that  
11:59:38 22 robust triglyceride reductions could be achieved but without  
11:59:45 23 perturbing the effect of the statin to control LDL-C, and  
11:59:49 24 there were other secondary and tertiary and exploratory goals  
11:59:54 25 of the study.

11:59:55 1 Q And are there any documents that describe the design of  
12:00:00 2 the ANCHOR study?

12:00:01 3 A Yes. One of the those would be the primary publication  
12:00:04 4 on the ANCHOR study by Dr. Christie Ballantyne.

12:00:07 5 Q And, Dr. Ketchum, I'll have you turn to Exhibit 942 in  
12:00:10 6 your binder. And, Dr. Ketchum, what is Exhibit 942?

12:00:20 7 A Exhibit 942 is the publication of the ANCHOR study  
12:00:27 8 results, primary study results, in the *American Journal of*  
12:00:33 9 *Cardiology*.

12:00:33 10 Q and are you familiar with Exhibit 942 from your work at  
12:00:35 11 Amarin?

12:00:36 12 A Yes, I am.

12:00:38 13 MS. KEANE: Your Honor, plaintiffs also move to  
12:00:40 14 admit Plaintiffs' Exhibit 942.

12:00:42 15 MR. KLEIN: No objection.

12:00:43 16 THE COURT: 942 is admitted.

12:00:43 17 (Plaintiffs' Exhibit 942 received in  
12:00:45 evidence.)

12:00:45 18 BY MS. KEANE:

12:00:46 19 Q Dr. Ketchum, where in Exhibit 942 is the design of the  
12:00:50 20 ANCHOR study discussed?

12:00:55 21 A So it's discussed in a number of places, but pictorially  
12:01:00 22 it's shown in Figure 1, the high level study design, page 2 of  
12:01:06 23 that article.

12:01:08 24 MS. KEANE: Mr. Brooks, if we could pull up  
12:01:11 25 Figure 1.

12:01:11 1 BY MS. KEANE:

12:01:12 2 Q And can you -- Dr. Ketchum, can you briefly describe the  
12:01:15 3 design of the ANCHOR study.

12:01:17 4 A Yes. Similar to the MARINE trial, it had a four- to  
12:01:21 5 six-week lead-in period, a two- to three-week qualifying  
12:01:26 6 period, and then after patients were determined whether or not  
12:01:30 7 they met the inclusion-exclusion criteria, those who did could  
12:01:34 8 be randomized one-to-one-to-one onto either of three treatment  
12:01:39 9 arms, placebo plus their stable statin dose, Vascepa 2-gram  
12:01:46 10 per day along with their stable statin dose, or Vascepa 4  
12:01:46 11 grams per day along with their stable statin dose.

12:01:52 12 And then they were followed across a 12-week  
12:01:55 13 double-blind period until the primary endpoint was -- and  
12:01:59 14 other measurements were made at the end of that 12-week  
12:02:02 15 period.

12:02:03 16 Q If we could turn to Figure 2 on page 3.

12:02:11 17 How many patients were involved in the ANCHOR study?

12:02:13 18 A There were a total of 702 patients randomized or enrolled  
12:02:19 19 into the ANCHOR study.

12:02:21 20 Q And can you describe the patient population studied in  
12:02:25 21 ANCHOR?

12:02:25 22 A Yes. This was a patient population, again, men and women  
12:02:31 23 aged 18 or older. They had to be willing to abide by the  
12:02:37 24 study schedule, same principle around diet and exercise that  
12:02:45 25 they needed to maintain throughout the trial. They needed to

12:02:48 1 agree to remain on their stable statin dose throughout the  
12:02:52 2 trial as well, and then, importantly, they needed to have  
12:02:56 3 fasting triglyceride levels between 200 and 499 milligrams per  
12:03:02 4 deciliter.

12:03:02 5 Q And why is it that patients in ANCHOR were required to be  
12:03:10 6 on a statin?

12:03:11 7 A Because of their lipid abnormality characterized by too  
12:03:17 8 high levels of bad cholesterol needing statin control.

12:03:22 9 Q And what were the results of the ANCHOR study?

12:03:27 10 A So ANCHOR -- the ANCHOR study met its prespecified  
12:03:35 11 primary and secondary and other endpoints, and characterized  
12:03:37 12 an acceptable safety and tolerability profile.

12:03:41 13 Q Are the results of ANCHOR reflected in Exhibit 942?

12:03:46 14 A Yes. This was the peer-reviewed publication  
12:03:53 15 communicating those primary efficacy and safety results.

12:03:57 16 Q And if we pull up Figure 3 in Exhibit 942.

12:04:01 17 What was the effect in ANCHOR of Vascepa 4 grams per  
12:04:12 18 day on triglycerides?

12:04:12 19 A As depicted in the dark shaded bar at the left hand of  
12:04:18 20 this histogram plot, Vascepa 4 grams per day on top of statin  
12:04:23 21 led to a 21.5 percent highly statistically significant  
12:04:29 22 reduction in triglycerides in the patients studied.

12:04:32 23 Q And what was the effect in ANCHOR on Vascepa 4 grams per  
12:04:39 24 day on LDL-C?

12:04:39 25 A So in addition to that degree of triglyceride reduction



12:04:46 1 relative to placebo, Vascepa 4 grams per day was associated  
12:04:47 2 with 6.2 percent reduction in bad cholesterol relative to  
12:04:54 3 placebo. That also was highly statistically significant.

12:04:58 4 Q What was the effect in ANCHOR of Vascepa 4 grams per day  
12:04:58 5 on apo B?

12:05:03 6 A The effect of Vascepa 4 grams per day on apo B relative  
12:05:07 7 to placebo was a 9.3 highly statistically significant  
12:05:14 8 reduction.

12:05:18 9 Q Dr. Ketchum, what is an SPA or a special protocol  
12:05:27 10 assessment?

12:05:28 11 A So an SPA or special protocol assessment is a regulatory  
12:05:36 12 process by which a sponsor can approach FDA and share its  
12:05:42 13 perspectives on the design and conduct of, in this case, a  
12:05:47 14 clinical development program to seek approval for a proposed  
12:05:52 15 indication. So it's a regulatory process that has specific  
12:05:58 16 requirements.

12:05:58 17 Q Did Amarin have an SPA with respect to the ANCHOR study?

12:06:04 18 A Yes, similar to MARINE and REDUCE-IT, Amarin had an SPA  
12:06:10 19 agreement for ANCHOR.

12:06:10 20 Q And, generally speaking, what were the terms of the SPA?

12:06:13 21 A Generally speaking the terms of that SPA were to conduct  
12:06:18 22 the ANCHOR study to have it meet its prespecified primary  
12:06:24 23 endpoint, that it also meet its endpoint to rule out a certain  
12:06:30 24 percentage rise in bad cholesterol, and that it characterized  
12:06:35 25 the safety profile, and that obviously would be a subject of

1 the subsequent review, but it clearly needed to have a safe  
2 and tolerable profile. That was one -- the whole conduct of  
3 ANCHOR was one component of the SPA agreement.

4 Other components were that the safety portion from  
5 ANCHOR needed to be submitted with the original NDA for FDA's  
6 review, and that the efficacy component of the ANCHOR study  
7 could not be submitted to FDA for its review until the large,  
8 long-term cardiovascular outcome study had been enrolled to  
9 the 50 percent point, and until that point, Amarin could not  
10 submit the supplemental new drug application for ANCHOR.

11 Q You reference a requirement with respect to LDL-C. Why  
12 was there a requirement with respect to LDL-C in the ANCHOR  
13 SPA?

14 A So again we're speaking about a patient population where  
15 their primary lipid abnormality is their bad cholesterol and  
16 needing control by the statin, and in the spirit of first do  
17 no harm, when you consider adding another therapy onto a  
18 statin, you -- you know, your medical intent is not to detract  
19 from the ability of that statin to exert its effect.

20 There are certain rules of thumb about the degree of  
21 increase in bad cholesterol that can lead to the need to  
22 double the statin dose. It's roughly in the 4 to 6 percent  
23 range, and so Amarin had to power its ANCHOR study to rule out  
24 that degree of rise. It's actually exceptionally overpowered  
25 on the triglyceride reduction. You can just see the

1 difference between MARINE, which had 220 patients, to have a  
2 robust powering for the triglyceride reduction endpoint, now  
3 we're talking about a 702 patient study.

4 The ANCHOR patient population and actually the power  
5 of that study was driven by the need to rule out the 4 to  
6 6 percent rise in bad cholesterol.

7 Q You also reference a requirement for a cardiovascular  
8 outcome study; is that right?

9 A Yes. So the -- as I mentioned before, statins had shown  
10 across a series of drug sponsored programs the ability to  
11 reduce cardiovascular risk by around 25 to 35 percent, and  
12 here we're talking about adding on another agent, and FDA  
13 required Amarin to have its cardiovascular outcomes trial far  
14 enough along that there would be -- to minimize the delay  
15 between the two study results.

16 Q And the cardiovascular outcome study you're referring to,  
17 is that REDUCE-IT?

18 A Yes, it's REDUCE-IT.

19 Q Did Amarin meet its obligations under the ANCHOR SPA?

20 A Yes, Amarin did.

21 Q Did Amarin submit an SNDA seeking an indication based on  
22 the ANCHOR study?

23 A Yes, it submitted that SNDA in approximately February of  
24 2013.

25 Q And just to be clear, what is an SNDA?

12:10:10 1 A The S stands for supplemental, and NDA stands for new  
12:10:16 2 drug application. You can't supplement an application until  
12:10:20 3 you have an approval of an original NDA.

12:10:23 4 Q And what was the proposed indication that Amarin was  
12:10:26 5 seeking in the SNDA?

12:10:28 6 A So in the ANCHOR SNDA Amarin was seeking a separate and  
12:10:34 7 distinct indication to reduce triglycerides and other lipid,  
12:10:41 8 lipoprotein, inflammatory marker parameters as an adjunct to  
12:10:47 9 statin therapy in patients with high triglycerides in the  
12:10:50 10 range of 200 to 499 milligrams per deciliter.

12:10:55 11 Q And did FDA approve the additional indication?

12:10:59 12 A No, FDA did not approve that proposed indication.

12:11:03 13 Q Do you have an understanding as to why that is?

12:11:07 14 A Yes, I do.

12:11:07 15 Q What is that understanding based on?

12:11:10 16 A On my firsthand responsibilities as the primary point of  
12:11:15 17 contact with the Food and Drug Administration.

12:11:17 18 Q And what is your understanding of why the ANCHOR  
12:11:23 19 indication was not approved?

12:11:25 20 A So FDA felt -- and this became apparent in the  
12:11:32 21 October 2013 time frame at our open public advisory committee  
12:11:40 22 meeting in which window of time FDA --

12:11:44 23 MR. KLEIN: I just want to lodge an objection to  
12:11:46 24 the extent he's going to offer hearsay. I can't tell whether  
12:11:51 25 he's going to, but it sounds like he might.

12:11:55 1 MS. KEANE: Your Honor, the question was for his  
12:11:57 2 understanding of why ANCHOR was not approved.

12:11:59 3 MR. KLEIN: Yeah, and I don't -- maybe he's not  
12:12:02 4 going to do it, but it sounded like he was going to relay  
12:12:05 5 conversations from the FDA.

12:12:06 6 THE COURT: Well, if his understanding is based  
12:12:09 7 on what he heard from other people, that would pose a hearsay  
12:12:12 8 concern, wouldn't it?

12:12:14 9 MS. KEANE: I think Dr. Ketchum -- and I'm happy  
12:12:16 10 to ask him additional questions -- testified that he was  
12:12:19 11 responsible for the proceedings back and forth with FDA  
12:12:24 12 relating to the ANCHOR indication, so I think he is intimately  
12:12:28 13 familiar with the correspondence and the issues.

12:12:32 14 THE COURT: Well, the objection is not his  
12:12:33 15 personal knowledge. The objection deals with how he obtained  
12:12:37 16 this information.

12:12:40 17 Certainly, I think he -- he started to testify  
12:12:43 18 as to his understanding, but then he stopped and explained --  
12:12:47 19 and I thought he was going to reference some meeting.

12:12:50 20 Perhaps he could just answer his understanding  
12:12:53 21 as to why the FDA did not approve the supplemental NDA based  
12:12:58 22 on -- for the ANCHOR study. Is there an objection to him  
12:13:02 23 answering that question?

12:13:03 24 MR. KLEIN: No. I mean, if the witness is going  
12:13:05 25 to refer to documents, and I don't know where you're going, if

12:13:08 1 you're going to some document where the FDA responded, I'm  
12:13:11 2 fine with that. But if the witness is going to relay  
12:13:14 3 conversation -- oral conversations from FDA people, I would  
12:13:17 4 object to that.

12:13:17 5 MS. KEANE: I don't think we need to get into a  
12:13:19 6 discussion of oral conversations that have been relayed.

12:13:23 7 THE COURT: All right. So you know the  
12:13:24 8 objection. Why don't you proceed.

12:13:25 9 MS. KEANE: Okay.

12:13:26 10 BY MS. KEANE:

12:13:26 11 Q So, Dr. Ketchum, turning back to the question, what is  
12:13:29 12 your understanding -- well, let me back up.

12:13:32 13 What is your -- do you have an understanding as to  
12:13:36 14 why FDA did not approve the indication?

12:13:39 15 A Yes, I have an understanding.

12:13:40 16 Q And what is that understanding based on?

12:13:42 17 A My understanding is based on the occurrences at the open  
12:13:49 18 public advisory committee hearing, and then, importantly,  
12:13:53 19 afterwards being sent a letter addressed to me officially  
12:13:57 20 rescinding the special protocol assessment agreement for  
12:14:02 21 ANCHOR in which they spelled out their reasons.

12:14:08 22 Q And what is your understanding as to why FDA did not  
12:14:14 23 approve the ANCHOR indication?

12:14:17 24 A So my understanding, as based on what I just described,  
12:14:23 25 is that there was scientific uncertainty caused by a series of

1 failed cardiovascular outcomes trials of other  
2 triglyceride-lowering agents that included a Fenofibrate  
3 compound in the ACCORD lipid trial, and two niacin containing  
4 products in the AIM HIGH and HPS2 THRIVE trials.

5 And the uncertainty was created by the fact that  
6 there were triglyceride, robust triglyceride reductions in  
7 those trials, but that each of those trials failed to meet  
8 their prespecified endpoint in the cardiovascular outcome  
9 trial.

10 Their view of ANCHOR and of Vascepa in this patient  
11 population was that one would only add Vascepa on top of the  
12 statin to further reduce cardiovascular risk, and that ANCHOR  
13 was clearly not designed in its 12-week trial context as a  
14 cardiovascular risk reduction trial, and, therefore, they  
15 pointed ahead to the need for the REDUCE-IT trial to be  
16 completed and reported to them for their review.

17 Q And I just wanted to clarify, I know you referred to a  
18 number of -- or a few failed outcome studies. You referred to  
19 one with respect to Fenofibrates; is that right?

20 A Yes.

21 Q And what study was that that you're referring to?

22 A That trial was referred to as ACCORD Lipid.

23 Q And did Amarin agree with FDA's decision not to approve  
24 the ANCHOR indication?

25 A No, it did not.

12:16:10 1 Q And how was FDA's decision conveyed to Amarin?

12:16:15 2 A It was conveyed on FDA letterhead in a letter to Amarin.

12:16:21 3 Q And after Amarin received that letter, what steps did  
12:16:26 4 Amarin take to respond to FDA's decision not to approve the  
12:16:32 5 ANCHOR indication?

12:16:33 6 A So that letter was issued by the Review Division, so the  
12:16:33 7 Division of Metabolic and Endocrinology products, or DMEP,  
12:16:33 8 D-M-E-P.

12:16:33 9 So what Amarin, after internal consultation, was  
12:16:56 10 required to do to interact with FDA was to request a formal  
12:16:57 11 reconsideration meeting at that division level, which it did,  
12:17:02 12 and then subsequently went up to two higher levels within FDA  
12:17:09 13 through a formal dispute resolution process.

12:17:13 14 Q And in the course of that appeal, those appeal processes,  
12:17:21 15 did Amarin make arguments to FDA with respect to the ANCHOR  
12:17:26 16 indication?

12:17:27 17 A Yes, it did.

12:17:27 18 Q And what arguments did Amarin present to FDA in support  
12:17:31 19 of its request for reconsideration?

12:17:33 20 A Well, firstly, that we had done everything in accordance  
12:17:38 21 with the agreement in terms of those various components that I  
12:17:42 22 mentioned previously in terms of having submitted the safety  
12:17:46 23 data as part of the original NDA, the efficacy data as part of  
12:17:51 24 the supplemental NDA, and a holding off on submitting that  
12:17:56 25 SNDA until we had our large, long term cardiovascular outcomes



12:18:02 1 trial 50 percent enrolled, and not only that, but that the  
12:18:06 2 results had read out robustly and consistently meeting all  
12:18:11 3 prespecified endpoints.

12:18:12 4 Q And did Amarin -- did Amarin state any evidence in  
12:18:16 5 support of its positions?

12:18:18 6 A Yes. So they communicated that there was scientific  
12:18:26 7 uncertainty because of failed cardiovascular outcomes trials  
12:18:30 8 of other agents.

12:18:32 9 So we felt they should be judging our data set on  
12:18:37 10 the basis of what we had submitted and not, you know, on the  
12:18:42 11 basis of these failed cardiovascular outcomes trials. So we  
12:18:47 12 stated arguments and stated positions about how they should  
12:18:53 13 view icosapent ethyl differently from Fenofibrate and niacin  
12:18:59 14 containing products as an example.

12:19:01 15 Q What is the JELIS study?

12:19:05 16 A The JELIS study is a Japanese study that was published in  
12:19:17 17 the 2007 time frame. It's a study of -- so it's a large  
12:19:21 18 cardiovascular outcomes trial conducted in a Japanese patient  
12:19:26 19 population with a commercially available purified EPA product  
12:19:34 20 manufactured by a Japanese company called Mochida.

12:19:38 21 Q And what were the results of JELIS?

12:19:40 22 A So the authors in *Lancet* reported that -- that Epadel,  
12:19:49 23 the name of the product, on top of statin therapy, and the  
12:19:54 24 Epadel dose was 1.8 grams per day, that in the patient  
12:20:00 25 population study it led to a 19 percent relative risk

12:20:05 1 reduction on their primary cardiovascular event endpoint.

12:20:11 2 Q At the time of Amarin's discussions with FDA regarding  
12:20:16 3 the ANCHOR indication, what were Amarin's views of JELIS?

12:20:21 4 A Amarin, you know, as the sponsor of an IND and new drug  
12:20:31 5 application, we're responsible for being conversant and  
12:20:36 6 current with the literature so we had seen the results.

12:20:40 7 We then found interesting in the sense of that, you  
12:20:48 8 know, there's a very mixed history with omega-3s in the  
12:20:53 9 cardiovascular outcomes domain, and also in this window of  
12:20:58 10 time where we're interacting with FDA on the ANCHOR SPA  
12:21:02 11 recision, there's other failed cardiovascular outcomes trials.

12:21:07 12 So this is a challenging space, and I think we noted  
12:21:10 13 it as having certain significant limitations, but having, you  
12:21:16 14 know, certain aspects that were worthy of pointing out to FDA  
12:21:24 15 as -- you know, with the benefit at that point in time of our  
12:21:28 16 MARINE and ANCHOR results in hand, we were able to fold  
12:21:34 17 certain aspects of JELIS into our arguments with FDA as  
12:21:38 18 amongst the reasons that they shouldn't rush to a decision to  
12:21:43 19 rescind the SPA.

12:21:46 20 Q And in the course of that process, did you gain an  
12:21:49 21 understanding of FDA's views of JELIS?

12:21:52 22 A Yes, we did.

12:21:53 23 Q And what is that understanding based on?

12:21:56 24 A It's based on formal communications from FDA via the  
12:22:02 25 reconsideration and formal dispute resolution process with

12:22:07 1 FDA.

12:22:07 2 Q And when you refer to formal communications, are you  
12:22:10 3 referring to documents?

12:22:12 4 A Yes, documents on FDA letterhead formerly sent to the  
12:22:19 5 regulatory point of contact at Amarin.

12:22:28 6 Q If we could take -- Dr. Ketchum, if you could turn to  
12:22:33 7 Exhibit 990 in your binder.

12:22:40 8 Do you recognize Exhibit 990?

12:22:43 9 A Yes, I do.

12:22:45 10 Q What is Exhibit 990?

12:22:49 11 A So Exhibit 990 is a communication from FDA addressed to  
12:22:57 12 me at Amarin, and it is communicating the fact that our  
12:23:05 13 appeal, this is to the Office of Drug Evaluation, too, so we  
12:23:10 14 had to go back to the Review Division for formal  
12:23:15 15 reconsideration before we were allowed to appeal to the next  
12:23:19 16 higher level within FDA, and this is the end result of their  
12:23:24 17 review denying our appeal.

12:23:27 18 MS. KEANE: Your Honor, plaintiffs move to admit  
12:23:30 19 Exhibit 990 into evidence.

12:23:31 20 MR. KLEIN: No objection.

12:23:31 21 THE COURT: 990 is admitted.

12:23:31 22 (Plaintiffs' Exhibit 990 received in  
12:23:34 23 evidence.)

12:23:34 23 BY MS. KEANE:

12:23:35 24 Q And, Dr. Ketchum, who, who authored Exhibit 990 or who  
12:23:43 25 signed Exhibit 990?

12:23:44 1 A So the director of the Office of Drug Evaluation 2 at  
12:23:50 2 this point in time was Dr. Curtis Rosebrow.

12:23:56 3 Q And where in Exhibit 990 does FDA discuss its views with  
12:24:02 4 respect to the JELIS study?

12:24:09 5 A It discusses them at a variety of points. It goes out by  
12:24:17 6 study, study-by-study, and discussion of JELIS appears --

12:24:28 7 Q If I could direct your attention to page 11.

12:24:31 8 A Sure. Page 11. Yep, there in the middle paragraph.

12:24:38 9 Q And what are FDA's views on the JELIS study?

12:24:43 10 A So Dr. Rosebrow is indicating a number of what he  
12:24:52 11 considers design limitations, saying that caution must be  
12:24:59 12 exercised on interpreting the JELIS findings, one of those  
12:25:03 13 reasons being it was an open label study.

12:25:06 14 And then he goes on to say a couple of aspects that  
12:25:12 15 in, you know, in his team's role in protecting the public  
12:25:17 16 health of citizens of the United States, he's pointing out  
12:25:21 17 certain limitations and focusing on a study conducted in Japan  
12:25:29 18 about potentially inadequate statin therapy.

12:25:33 19 And then he mentions that one of the components of  
12:25:38 20 the cardiovascular end -- kind of endpoint composite considers  
12:25:45 21 more subjective than some of the other major adverse  
12:25:50 22 cardiovascular event endpoints.

12:25:54 23 And then he goes on to say that the positive results  
12:26:02 24 on that cardiovascular endpoint are contrasted by the fact  
12:26:06 25 that triglycerides were not decreased by a substantial amount

12:26:11 1 so views the trial as supportive.

12:26:17 2 Q So if you're -- you referred to a subjective endpoint.

12:26:24 3 What endpoint are you referring to?

12:26:25 4 A Dr. Rosebrow cites unstable angina, which a simpler term  
12:26:33 5 is chest pain.

12:26:35 6 Q And you referred to a subjective endpoint. What does  
12:26:40 7 that mean, a subjective endpoint?

12:26:42 8 A So subjective, so this endpoint is an endpoint that  
12:26:50 9 classically requires hospitalization. So an individual  
12:26:56 10 presenting with chest pain -- not all individuals presenting  
12:27:00 11 with chest pain -- some of them will not require  
12:27:04 12 hospitalization.

12:27:05 13 An open label trial can potentially introduce bias  
12:27:10 14 because if someone interviewing the patient is understanding  
12:27:16 15 that they're on multiple medications, it might incline them to  
12:27:21 16 hospitalize them more so than not being informed of that  
12:27:26 17 information.

12:27:26 18 So there's -- there's some subjectively by virtue of  
12:27:31 19 the open label nature with the hospitalization requirement,  
12:27:35 20 and it's also less objective than something like  
12:27:44 21 cardiovascular death.

12:27:50 22 Q And after receiving Plaintiffs' Exhibit 990, how did  
12:27:58 23 Amarin respond?

12:28:01 24 A So Amarin regrouped. There's a lot of information  
12:28:05 25 contained in this appeal denial. And then it had to weigh the

12:28:12 1 pros and cons of deciding whether or not to appeal to the next  
12:28:15 2 level, which it did in appealing to the Office of New Drugs,  
12:28:22 3 the next higher level within FDA.

12:28:27 4 Q And did FDA change its mind with respect to refusing to  
12:28:32 5 approve the ANCHOR indication?

12:28:34 6 A No. FDA did not in that subsequent appeal step, and also  
12:28:42 7 consulted the Office of New Drugs, extended the time frame for  
12:28:50 8 the appeal process, consulted with an even higher level within  
12:28:56 9 FDA called the Medical Policy Council which is comprised of  
12:29:00 10 senior leadership within FDA, and then ultimately denied  
12:29:05 11 Amarin's appeal at that level.

12:29:08 12 So we received a similar letter but from the  
12:29:14 13 director of the Office of New Drugs after that.

12:29:18 14 Q Okay. And then after receiving the letter from the  
12:29:22 15 Office of New Drugs, what steps did Amarin take?

12:29:26 16 A So Amarin again had another rather lengthy letter to  
12:29:31 17 assimilate and to discuss the pros and cons, because Office of  
12:29:37 18 New Drugs had consulted even more senior FDA leadership as  
12:29:43 19 part of conveying the appeal denial. We ultimately decided  
12:29:47 20 not to appeal to the next higher level.

12:29:51 21 Q And did Amarin take any additional steps after deciding  
12:29:56 22 not to appeal again?

12:29:57 23 A Yes. So then Amarin took a First Amendment approach to  
12:30:04 24 try to obtain the right to truthfully and nonmisleadingly  
12:30:11 25 promote the ANCHOR study results.

12:30:14 1 Q Okay. And in -- well, what type of proceeding was that?

12:30:21 2 A That was a First Amendment legal proceeding.

12:30:25 3 Q Okay. And were FDA's views reflected -- I'm sorry, were  
12:30:31 4 FDA reviews from that proceeding reflected?

12:30:36 5 A In the FDA senior official declaration that was made.

12:30:45 6 MS. KEANE: And, Mr. Brooks, we can take down, I  
12:30:47 7 think, Plaintiffs' Exhibit 990.

12:30:47 8 BY MS. KEANE:

12:30:51 9 Q And did FDA maintain its positions with respect to JELIS  
12:30:55 10 in the First Amendment litigation?

12:30:59 11 A Yes, FDA did.

12:31:00 12 Q And did FDA also maintain its positions with respect to  
12:31:03 13 the ANCHOR indication during the First Amendment proceeding?

12:31:10 14 A So FDA did not overturn its decision about rescinding the  
12:31:18 15 ANCHOR indication, but through that process it did agree with  
12:31:24 16 the characterization of the safety and efficacy results as  
12:31:31 17 reported by Amarin through that process.

12:31:33 18 Q And where are FDA's views from the First Amendment  
12:31:37 19 proceeding reflected?

12:31:38 20 A They're reflected in Dr. Curtis Rosebrow's declaration.

12:31:43 21 Q If we could turn to Exhibit 990 -- I'm sorry, 994 in your  
12:31:49 22 binder. And what is Exhibit 994?

12:32:01 23 A That is Dr. Curtis Rosebrow's declaration for the First  
12:32:05 24 Amendment lawsuit.

12:32:09 25 Q And are you familiar with Director Rosebrow's

12:32:11 1 declaration?

12:32:11 2 A Yes, I am.

12:32:12 3 MS. KEANE: Okay. Your Honor, plaintiffs move  
12:32:14 4 to admit Plaintiffs' Exhibit 994 into evidence.

12:32:19 5 MR. KLEIN: No objection.

12:32:20 6 THE COURT: 994 is admitted.

12:32:20 7 (Plaintiffs' Exhibit 994 received in  
12:32:20 8 evidence.)

12:32:20 8 BY MS. KEANE:

12:32:28 9 Q And, Dr. Ketchum, what is your understanding of FDA's  
12:32:36 10 views on JELIS based on Dr. Rosebrow's declaration?

12:32:40 11 A That they maintained their stance that there were  
12:32:48 12 significant design flaws or limitations in the JELIS study.

12:32:53 13 Q And what was the effect of FDA's decision not to approve  
12:32:58 14 the ANCHOR indication on Amarin?

12:33:01 15 A It had an extremely significant impact on Amarin, both  
12:33:09 16 immediately -- in the fourth quarter of 2013 as we received  
12:33:16 17 the formal communication from FDA rescinding the ANCHOR  
12:33:23 18 special protocol assessment agreement, we had to let  
12:33:23 19 approximately 50 percent of our workforce go.

12:33:27 20 You know, really an -- atypical and unprecedented  
12:33:37 21 situation of an SPA being rescinded, we obviously had devised  
12:33:42 22 the three-part clinical program with each study leading to  
12:33:48 23 successively expanded indications and had built a business  
12:33:54 24 model whereby those expanded indications, assuming they would  
12:34:00 25 be approved, would likely lead to increased revenue for the



12:34:04 1 business that would enable us to -- not just to grow in  
12:34:08 2 general, but also to offset the cost of the very expensive,  
12:34:13 3 large, long-term REDUCE-IT study.

12:34:18 4 Q If we could turn now to the REDUCE-IT study. Can you  
12:34:24 5 briefly describe the REDUCE-IT study.

12:34:27 6 THE COURT: And, Ms. Keane, before you move to  
12:34:28 7 the REDUCE-IT study, do you think this is a good time to take  
12:34:32 8 our lunch break?

12:34:33 9 MS. KEANE: That would be great from my  
12:34:33 10 perspective.

12:34:34 11 THE COURT: All right. We'll take -- I think we  
12:34:36 12 agreed on a 30-minute lunch break. We'll take our lunch break  
12:34:40 13 at this time.

12:34:41 14 Thank you.

12:34:41 15 (The noon recess was taken.)

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01:08:58 4 THE COURT: Ms. Keane, you ready to resume?

01:08:59 5 MS. KEANE: Yes, Your Honor.

01:08:59 6 DIRECT EXAMINATION RESUMED

01:08:59 7 BY MS. KEANE:

01:09:01 8 Q Dr. Ketchum, I just wanted to ask a few follow-up  
01:09:04 9 questions about a few things we discussed this morning.

01:09:08 10 MS. KEANE: Mr. Brooks, can you pull up  
01:09:11 11 Plaintiffs' Exhibit 1186, the Vascepa prescribing information.  
01:09:17 12 If you could turn to Section 14.2, and specifically if we  
01:09:24 13 could go to page 11 with the results from the MARINE study.  
01:09:29 14 Could you pull up Table 2.

01:09:29 15 BY MS. KEANE:

01:09:35 16 Q Dr. Ketchum, when are -- with respect to the MARINE  
01:09:39 17 study, when were baseline triglycerides levels measured?

01:09:43 18 A At baseline following randomization into the study.

01:09:50 19 Q Okay. And when was diet and lifestyle, the diet and  
01:09:54 20 lifestyle stabilization period initiated as it relates to the  
01:10:00 21 baseline measurements?

01:10:01 22 A In the weeks prior to randomization.

01:10:05 23 Q And how long prior to randomization?

01:10:08 24 A So there was a four- to six-week diet and lifestyle  
01:10:14 25 lead-in, and then a two- to three-week qualifying period, so

01:10:18 1 that's like six to nine weeks in advance of randomization.

01:10:22 2 Q And did that diet and lifestyle time period apply to each  
01:10:27 3 of the arms of the MARINE study?

01:10:29 4 A Yes, it did. It applied to all patients.

01:10:32 5 Q So that would include patients who received placebo as  
01:10:37 6 well?

01:10:37 7 A Yes.

01:10:37 8 Q And then the comparison, the results that are shown in  
01:10:44 9 Table 2, are those results based on a comparison between a  
01:10:51 10 placebo group that received diet and lifestyle as compared to  
01:10:57 11 individuals on the -- with the active ingredient also on diet  
01:11:01 12 and lifestyle?

01:11:02 13 A Yes, specifically at the 12-week primary efficacy  
01:11:06 14 endpoint.

01:11:06 15 Q I want to spend some time now talking about the REDUCE-IT  
01:11:15 16 study. Could you briefly describe for us the REDUCE-IT study.

01:11:22 17 A Yes. REDUCE-IT was a large, long-term cardiovascular  
01:11:26 18 outcome study looking at patients who were on a statin, but,  
01:11:31 19 in spite of that, had elevated triglycerides in the range of  
01:11:34 20 200 hundred to 499. Actually, the enrollment criteria was 150  
01:11:39 21 to 499 milligrams per deciliter. And they had other  
01:11:44 22 characteristics, either established cardiovascular disease or  
01:11:48 23 other risk factors.

01:11:49 24 And this was a study conducted across 11 countries,  
01:11:54 25 hundreds of sites, total of over 8,000 patients, and they were

1 followed across a median of 4.9 years to follow the occurrence  
2 of cardiovascular events.

3 Q What was the medical rationale for the REDUCE-IT study?

4 A So the medical rationale was that there was an un-met  
5 medical need that, in spite of the advances of statin therapy,  
6 that patients still have approximately 65 to 75 percent  
7 residual risk, and they need other therapies to help address  
8 that residual risk.

9 Q Can you briefly describe the resources that Amarin  
10 devoted to REDUCE-IT.

11 A Yes. So including the planning and design phase, this  
12 was a decade-plus process, and of that total of \$500 million  
13 that I mentioned for the three-part clinical program,  
14 approximately \$300 million were deployed in the direction of  
15 REDUCE-IT.

16 Q And was REDUCE-IT successful?

17 A REDUCE-IT was successful. It met all of its primary, key  
18 secondary, and other endpoints.

19 Q Are there documents that describe the design of the  
20 REDUCE-IT study?

21 A Yes. We published a design paper in *Clinical Cardiology*.

22 Q If you could turn to Exhibit 30 -- I'm sorry, Exhibit 439  
23 in your binder. And what is Exhibit 439?

24 A That's the 2017 design paper in *Clinical Cardiology* for  
25 REDUCE-IT.

01:13:37 1 Q And are you one of the coauthors of Exhibit 439?

01:13:40 2 A Yes, I am.

01:13:43 3 MS. KEANE: Your Honor, plaintiffs move to admit  
01:13:45 4 Plaintiffs' Exhibit 439 into evidence.

01:13:47 5 MR. KLEIN: No objection.

01:13:48 6 THE COURT: 439 is admitted.

01:13:48 7 (Plaintiffs' Exhibit 439 received in  
01:13:52 evidence.)

01:13:52 8 BY MS. KEANE:

01:13:54 9 Q Dr. Ketchum, where in Exhibit 439 is the design of the  
01:13:58 10 REDUCE-IT study discussed?

01:14:00 11 A It's presented in the Figure 1 on page 2 of the article  
01:14:07 12 in a study design figure.

01:14:11 13 MS. KEANE: Mr. Brooks, if we could pull up  
01:14:14 14 Figure 1.

01:14:14 15 BY MS. KEANE:

01:14:15 16 Q Dr. Ketchum, what was the patient population that was  
01:14:18 17 studied in REDUCE-IT?

01:14:20 18 A So as indicated at the top of the design figure, this was  
01:14:24 19 a study of men and women aged 45 years or older who needed to  
01:14:30 20 be on statin for their bad cholesterol, and then the patients  
01:14:36 21 additionally needed to either have established cardiovascular  
01:14:41 22 disease, meaning a prior heart attack, stroke, et cetera.

01:14:46 23 This represented approximately 70 percent of the  
01:14:48 24 patients enrolled into REDUCE-IT with the remainder qualifying  
01:14:52 25 on the basis of having diabetes mellitus and at least one

01:14:59 1 additional risk factor.

01:15:00 2 And in terms of lipid criteria, on a fasting  
01:15:07 3 triglyceride basis, they needed to have triglycerides in the  
01:15:11 4 range of 150 milligrams per deciliter to 499 milligrams per  
01:15:17 5 deciliter, and they needed to have their bad cholesterol  
01:15:22 6 controlled in the range of 41 milligrams per deciliter to  
01:15:26 7 100 milligrams per deciliter.

01:15:29 8 Q So you mentioned triglyceride levels. Were there  
01:15:32 9 patients in the REDUCE-IT study who had triglyceride levels  
01:15:37 10 above 500 milligrams per deciliter?

01:15:40 11 A Yes, there were.

01:15:41 12 Q Could you briefly describe -- well, actually, let me back  
01:15:45 13 up.

01:15:45 14 Can you explain why it's the case that there are  
01:15:48 15 patients with triglyceride levels above 500 milligrams per  
01:15:53 16 deciliter who were in the study?

01:15:55 17 A Yes. So during the screening period the patients were  
01:15:58 18 determined to be eligible for the study if they had a fasting  
01:16:02 19 triglyceride measurement in the ranges depicted in that  
01:16:07 20 shadowed -- shaded box.

01:16:09 21 But patients' triglycerides do fluctuate, that's a  
01:16:15 22 well-known phenomenon, and patients were determined based on  
01:16:21 23 their qualifying measurement, but then when they were  
01:16:24 24 randomized, it's the baseline measurement that gets reported  
01:16:28 25 for all of the key efficacy results.

01:16:31 1 And there were patients both above 500 milligrams  
01:16:36 2 per deciliter and below the lower end of the triglyceride  
01:16:40 3 range following randomization and upon evaluation of their  
01:16:47 4 base-line measurement.

01:16:49 5 Q So if you can turn to Figure 1, could you briefly  
01:16:51 6 describe the design of the REDUCE-IT study.

01:16:53 7 A Yes. So REDUCE-IT, during the screening period, it  
01:16:58 8 involved a lead-in where patients were ensured to be  
01:17:02 9 stabilized on their statin. Again, they were washed out of  
01:17:06 10 any other lipid-altering medications, so as to not confound  
01:17:10 11 the ability to determine the incremental effect of the Vascepa  
01:17:14 12 on top of the statin.

01:17:15 13 And then they -- as I mentioned before, they had  
01:17:18 14 some lipid qualification measurements. If they met the  
01:17:22 15 inclusion/exclusion criterion, then they were able to be  
01:17:26 16 randomized one-to-one to receive either icosapent ethyl  
01:17:32 17 Vascepa, 4 grams per day, on top of their statin, or a  
01:17:36 18 placebo, a matching placebo on top of their statin.

01:17:40 19 And then there were scheduled visits across the  
01:17:42 20 subsequent years until the end of the study.

01:17:45 21 After a certain number of primary cardiovascular  
01:17:48 22 endpoints had been accrued, then that was the end of the  
01:17:52 23 study, and the primary endpoint is listed there at the bottom  
01:17:56 24 of that slide.

01:17:57 25 Q And what was the primary endpoint of REDUCE-IT?

01:18:00 1 A It was the time from randomization to the first  
01:18:04 2 occurrence of any one of five major adverse cardiovascular  
01:18:09 3 events, specifically cardiovascular death, non-fatal  
01:18:12 4 myocardial infarction, also known as heart attack, non-fatal  
01:18:18 5 stroke, coronary revascularization, or unstable angina  
01:18:24 6 requiring hospitalization.

01:18:25 7 Q Were there any secondary endpoints in REDUCE-IT?

01:18:28 8 A Yes. There was a prespecified key secondary endpoint  
01:18:33 9 that focused on three composite major adverse cardiovascular  
01:18:37 10 events, and then there were other secondary, tertiary, and  
01:18:43 11 exploratory endpoints.

01:18:45 12 Q Are there documents that describe the results from  
01:18:47 13 REDUCE-IT?

01:18:48 14 A Yes. The results are described within the clinical study  
01:18:53 15 report and in a primary results publication that we made in  
01:18:59 16 *The New England Journal of Medicine*.

01:19:02 17 Q Okay. If we could turn to Plaintiffs' Exhibit 1189 in  
01:19:05 18 your binder.

01:19:11 19 MS. KEANE: And, Your Honor, just for the  
01:19:12 20 record, again, I just want to note that Plaintiffs'  
01:19:16 21 Exhibit 1189 is one that we would request time to redact  
01:19:22 22 before it's made publically available.

01:19:22 23 BY MS. KEANE:

01:19:25 24 Q Do you recognize Exhibit 1189, Dr. Ketchum?

01:19:27 25 A Yes, I do.



01:19:28 1 Q And what is Exhibit 1189?

01:19:30 2 A That Exhibit 1189 is the final clinical study report for  
01:19:36 3 the REDUCE-IT study.

01:19:37 4 Q And what role did you play in compiling the REDUCE-IT  
01:19:42 5 clinical study report?

01:19:43 6 A As reflected on the next page, on page 2 of the clinical  
01:19:48 7 study report, I was one of the reviewers and signatories of  
01:19:54 8 the document.

01:19:56 9 MS. KEANE: Your Honor, plaintiffs move to admit  
01:19:58 10 Exhibit 1189 into evidence.

01:20:00 11 MR. KLEIN: No objection.

01:20:01 12 THE COURT: 1189 is admitted.

01:20:01 13 (Plaintiffs' Exhibit 1189 received in  
01:20:04 evidence.)

01:20:04 14 BY MS. KEANE:

01:20:05 15 Q Dr. Ketchum, could you please turn to Exhibit 272 in your  
01:20:09 16 binder. What is Exhibit 272?

01:20:14 17 A Exhibit 272 is our publication of the primary results of  
01:20:25 18 REDUCE-IT in *The New England Journal of Medicine*.

01:20:28 19 Q Okay. And, again, you're listed as an author on  
01:20:31 20 Exhibit 272?

01:20:31 21 A Yes, I am.

01:20:33 22 MS. KEANE: Your Honor, plaintiffs move to admit  
01:20:35 23 Exhibit 272 into evidence.

01:20:36 24 MR. KLEIN: No objection.

01:20:38 25 THE COURT: 272 is admitted as well.

(Plaintiffs' Exhibit 272 received in evidence.)

BY MS. KEANE:

Q And where in Exhibit 272 are the results of REDUCE-IT discussed?

A They're discussed beginning on the third page of the publication and those primary and key secondary endpoints results are depicted in Figure 1 on page 5 of the publication.

MS. KEANE: Mr. Brooks, can we pull up Figure 1, specifically, Figure 1A.

BY MS. KEANE:

Q Dr. Ketchum, can you explain what Figure 1A depicts.

A Yes. So this is a graphical depiction of the prespecified primary endpoint of the REDUCE-IT clinical trial.

The inset is just a further magnification of the graphical display that occurs on the outside, and the horizontal axis is the year since patients were randomized into the trial. So time is increasing, moving to the right.

And the number -- excuse me, the percentage of patients with major adverse cardiovascular event are depicted on the vertical axis.

And what it's showing are the two treatment arms in the REDUCE-IT study. So, the placebo plus statin arm is depicted by the dotted red line, and the Vascepa, or icosapent ethyl plus statin arm is depicted by the solid blue line.

And what it's showing is the accrual of those -- you

1 know, the difference in the events between those two treatment  
2 arms, and the results are expressed as -- so you can see by  
3 virtue of the placebo curve being on top of the Vascepa curve,  
4 that the greater percentage of events occurred in the one drug  
5 arm than in the two drug arms.

6 And the way that those results are expressed are as  
7 a hazard ratio which is, basically, just converted. So it's  
8 expressed to zero -- a hazard ratio of 0.75, that means there  
9 was a 25 percent relative risk reduction in the pre-specified  
10 primary endpoint.

11 MS. KEANE: And, Mr. Brooks, if we could pull up  
12 Figure 1B.

13 BY MS. KEANE:

14 Q Dr. Ketchum, could you explain what is depicted in  
15 Figure 1B.

16 A Yes. So this is the same type of plot. It's called a  
17 Kaplan-Meier plot, and this time, as opposed to the time to  
18 the first occurrence of any one of five types of major adverse  
19 cardiovascular event, this plot is focused on the times of the  
20 first occurrence of any one of three major adverse  
21 cardiovascular events; specifically, cardiovascular death,  
22 non-fatal myocardial infarction, and non-fatal stroke.

23 And, again, the results are expressed as a hazard  
24 ratio, so in this instance there was a 26 percent relative  
25 risk reduction observed by virtue of Vascepa on top of statin

therapy.

Q And if we could turn to Figure 4 on page 10.

And, Dr. Ketchum, what is shown on Figure 4 on page 10?

A So Figure 4 is a different type of graphical transformation of the efficacy data in REDUCE-IT. It's called a Forest plot, and it's depicting graphically the hazard ratio.

So as I mentioned before, in the first row, the top row, that's the pre-specified primary five component, major adverse cardiovascular event, where a 25 percent relative risk reduction was observed.

The second row is presenting the key secondary endpoint results. And these are listed in what's known as a statistical hierarchy.

So, as part our special protocol assessment agreement with FDA, we had to, in essence, pre-declare our criteria by determining -- for determining success at the trial, and we had to list these in a specific order, and according to the statistical analyses, you could not move from the top row, to the second, to the third, fourth, et cetera, without the prior endpoint having met the criteria and first statistical significance, which is listed at the far right in the P value column.

And as reflected here, there was robustness,

01:25:38 1 consistency in the sequential order within the prespecified  
01:25:43 2 statistical hierarchy. The only endpoint not achieving that  
01:25:48 3 significance was death from any cause in the bottom row.

01:25:53 4 Q And you had previously mentioned a 25 percent risk  
01:25:56 5 reduction with respect to the primary endpoint; is that right?

01:26:00 6 A Yes.

01:26:00 7 Q And what does a 25 percent reduction mean for our  
01:26:07 8 patients?

01:26:08 9 A So to address that, I'll make a couple of comments to  
01:26:14 10 hopefully put it in perspective.

01:26:16 11 One is that, as I mentioned earlier, there had been  
01:26:19 12 a range of statin drugs developed by a series of drug  
01:26:23 13 companies over a number of years that had shown anywhere from  
01:26:27 14 25 to 35 percent cardiovascular risk reduction.

01:26:32 15 So patients only on a statin therapy have about that  
01:26:38 16 much to hope for in terms of their ability to have their  
01:26:43 17 cardiovascular risk reduced. That leaves 65 to 75 percent  
01:26:47 18 remaining. So to have 25 percent of that on top of the statin  
01:26:51 19 therapy addressed by virtue of another agent is very  
01:26:55 20 significant indeed.

01:26:57 21 Q And one of the studies we talked about earlier today was  
01:27:01 22 JELIS. How did the REDUCE-IT results compare to JELIS?

01:27:06 23 A So they were more robust and consistent across the series  
01:27:17 24 of endpoints described on this slide as one example. And, you  
01:27:25 25 know, in addition, there was a -- you know, a very well

1 characterized safety profile that was, you know, very well  
2 established, and in a multi-national patient population.

3 So in comparing and contrasting to JELIS, that's an  
4 important consideration that patients from 11 countries were  
5 involved in this trial, so a broader patient population was  
6 enrolled.

7 And also, this trial had the benefit of a placebo  
8 arm, which was one of the significant criticisms of the JELIS  
9 trial.

10 Q Did Amarin pursue an additional -- well, did Amarin  
11 pursue an additional indication based on REDUCE-IT?

12 A Yes. By virtue of having met the conditions of the  
13 special protocol assessment agreement, we proceeded with an  
14 SNDA submission in March 2019.

15 Q And after Amarin's submission in March of 2019, what  
16 happened with respect to that submission?

17 A So when a sponsor submits a supplemental new drug  
18 application, there's a period during which the FDA is  
19 determining whether it should be accepted for filing, whether  
20 it's complete in terms of all the electronic and other  
21 components that are submitted.

22 So, that occurred, and then Amarin was formally  
23 notified of the official acceptance of the application, and  
24 that it had been granted priority review.

25 And then subsequent to that acceptance period, the

review team then goes into -- begins its detailed review of the submitted information, and during that period of time they start to review and have questions for the sponsor, and they also make a determination as to whether or not they need an open public FDA advisory committee meeting.

In our case, for this SNDA, they determined the need for such an open public forum, which occurred in November of 2019, and then FDA, after convening that forum, which led to a 16 to zero favorable vote in favor of an expanded indication based on REDUCE-IT, the FDA completed its review and then approved Vascepa for that expanded indication in December of 2019.

MS. KEANE: Okay. And, Mr. Brooks, if we could go to Exhibit 1186, and if we could turn to page 2 and pull up the indications.

BY MS. KEANE:

Q And, Dr. Ketchum, we discussed earlier today the first indication listed on Exhibit 1186 is the REDUCE-IT indication?

A Yes, the first bullet point is the REDUCE-IT indication.

Q And what triglyceride levels does the indication cover?

A Elevated triglyceride levels greater than or equal to 150 milligrams per deciliter.

Q And does that also include patients with triglyceride levels above 500 milligrams per deciliter?

A Yes, it does.

01:30:59 1 Q You'll see the indication also refers to a maximally  
01:31:03 2 tolerated statin therapy? Do you see that?

01:31:06 3 A Yes.

01:31:06 4 Q What does maximally tolerated statin therapy mean?

01:31:10 5 A So it means that patients can be on a range of statins,  
01:31:16 6 on statin doses to control their bad cholesterol, and so  
01:31:21 7 that -- that medical reality is factored into that statement,  
01:31:28 8 but also that some patients cannot tolerate statins, and some  
01:31:32 9 patients are unwilling to go onto statins. So it encompasses  
01:31:38 10 all three of those aspects.

01:31:39 11 Q Now, if we could turn to Defendants' Exhibit 2247.

01:32:01 12 Do you recognize Defendants' Exhibit 2247?

01:32:05 13 A Yes. This is the approved prescribing information for  
01:32:11 14 Vascepa as of March 2019.

01:32:14 15 Q Okay. If you could take a look at the indications. I  
01:32:19 16 believe you just referred to it as the approved prescribing --

01:32:23 17 A I apologize. There's no cover page indicating.

01:32:26 18 This is the version -- we submitted a supplemental  
01:32:29 19 new drug application in March of 2019. As part of the SNDA,  
01:32:35 20 we're required, as the sponsor, to submit our proposed -- our  
01:32:42 21 proposed prescribing information in a specific format, and  
01:32:47 22 it's submitted in this form without any other, you know, draft  
01:32:54 23 watermarks or anything like that, but it is a draft proposed  
01:32:58 24 prescribing information.

01:32:59 25 MS. KEANE: Okay. And, Mr. Brooks, if we could



01:33:02 1 turn to Section 6.2 --

01:33:05 2 THE COURT: I'm sorry. Did you reference  
01:33:07 3 Exhibit 2247?

01:33:08 4 MS. KEANE: Yes, Your Honor.

01:33:09 5 THE COURT: Plaintiff or defendant?

01:33:12 6 MS. KEANE: Defendants'.

01:33:15 7 THE COURT: Thank you.

01:33:15 8 BY MS. KEANE:

01:33:17 9 Q If we could pull up Section 6.2, the postmarketing  
01:33:22 10 experience.

01:33:22 11 Dr. Ketchum, do you see in Section 6.2 there's a  
01:33:28 12 reference there to a chronic care population. Do you see  
01:33:34 13 that?

01:33:34 14 A Yes, in the second sentence.

01:33:37 15 Q And what is that a reference to?

01:33:39 16 A So, again, this is in the context of a proposed label.  
01:33:46 17 This is one of the required sections.

01:33:48 18 We already had an approved indication that had been  
01:33:51 19 marketed for some time, so we had an obligation to list out  
01:33:55 20 proposed adverse reactions that should be reflected in the  
01:34:00 21 revised label, and we're reflecting that that existing  
01:34:03 22 approved indication is for a chronic indication.

01:34:13 23 Q And when Amarin refers to the population in the draft  
01:34:17 24 labeling, what is that population or reference to?

01:34:20 25 A That's the MARINE population.

01:34:23 1 Q And why did -- why did Amarin describe the MARINE  
01:34:28 2 population as a chronic care population?

01:34:31 3 A It's a factually accurate characterization of the patient  
01:34:37 4 population in the MARINE study and indication.

01:34:41 5 Q All right. And is the phrase "chronic care population"  
01:34:45 6 present in the final version of the Vascepa approved labeling?

01:34:52 7 A No, it is not.

01:34:53 8 Q All right. And why not?

01:34:54 9 A So I don't know specifically, in that in the labeling  
01:35:03 10 comments provided by FDA it was a strike-through comment, so I  
01:35:09 11 have no additional direct feedback from FDA in the  
01:35:14 12 communication sent to us.

01:35:20 13 So in my evaluation, it was felt that it was  
01:35:23 14 sufficiently --

01:35:24 15 MR. KLEIN: Objection. Calls for speculation.

01:35:28 16 MS. KEANE: Well, let me see if I can rephrase  
01:35:32 17 the question?

01:35:32 18 THE COURT: Yes.

01:35:33 19 MS. KEANE: Okay.

01:35:33 20 BY MS. KEANE:

01:35:34 21 Q And, Dr. Ketchum, do you have an understanding as to why  
01:35:37 22 the "chronic care population" phrase is not in the final  
01:35:41 23 version of labeling?

01:35:42 24 MS. KEANE: Same objection. He testified that  
01:35:45 25 FDA didn't tell him, so he's just going to speculate.

01:35:49 1 THE COURT: Ms. Keane, what's your response?

01:35:52 2 MS. KEANE: I think that based on Dr. Ketchum's  
01:35:56 3 experience and his familiarity with the discussions with FDA,  
01:36:00 4 that he has an understanding as to why the labeling does  
01:36:07 5 not -- why the phrase is not included in the final labeling.  
01:36:10 6 He's involved in the labeling discussions back and forth with  
01:36:14 7 FDA.

01:36:14 8 THE COURT: If that's the position, I think you  
01:36:16 9 need to lay some more foundation, because without that  
01:36:18 10 additional foundation, seems to me like he's being asked to  
01:36:22 11 speculate as to why the FDA did not approve that additional  
01:36:25 12 language.

01:36:26 13 MS. KEANE: Okay. And I can ask a few  
01:36:27 14 additional questions.

01:36:28 15 BY MS. KEANE:

01:36:29 16 Q Dr. Ketchum, were you involved with the labeling  
01:36:32 17 discussions with FDA relating to the final Vascepa approved  
01:36:38 18 labeling?

01:36:39 19 A Yes, I was.

01:36:39 20 Q And what was your role in those discussions?

01:36:41 21 A I was an integral part of the team interacting with FDA  
01:36:48 22 on all of these labeling interactions.

01:36:51 23 Q And did you review the various versions of the labelings  
01:36:54 24 that were exchanged back and forth between Amarin and FDA?

01:36:57 25 A Yes, I did.

01:36:58 1 Q Could you actually tell us a little bit about the process  
01:37:02 2 as to how the labeling is, I guess, discussed between Amarin  
01:37:09 3 and FDA.

01:37:10 4 A Yes. So that earlier version that we -- the defendants'  
01:37:17 5 exhibit that we walked through that was the proposed version  
01:37:20 6 of the label that we submitted to FDA, at -- post the advisory  
01:37:27 7 committee meeting, in the final weeks, when they're  
01:37:34 8 determining that they're going to move in a favorable  
01:37:36 9 direction towards approval, and really never before then, FDA  
01:37:41 10 will start to interact with the sponsor and share by e-mail, a  
01:37:47 11 strike through addition, sometimes with comment boxes,  
01:37:51 12 depending on whether they feel they need to elaborate on the  
01:37:55 13 strike-through or the addition.

01:37:57 14 That's sent by e-mail to the regulatory affairs to a  
01:38:01 15 single point of contact within Amarin who reports in through  
01:38:05 16 me, and then we assemble a team to evaluate FDA's feedback,  
01:38:11 17 and then it's an iterative process.

01:38:14 18 So classically, there's two or three such iterations  
01:38:18 19 back and forth between a sponsor --

01:38:21 20 Q And --

01:38:21 21 A -- and in this instance, they struck through "chronic  
01:38:29 22 care population."

01:38:33 23 Q And I believe, as you've mentioned before that -- well,  
01:38:38 24 let me back up.

01:38:39 25 Did FDA provide a comment with respect to the

01:38:41 1 strike-through for chronic care?

01:38:43 2 A Not for this particular comment.

01:38:46 3 Q And based on your experience with respect to labeling  
01:39:00 4 negotiations, do you have an understanding as to why FDA does  
01:39:03 5 not include comments with strike-throughs?

01:39:06 6 THE COURT: Are you asking in general or --

01:39:08 7 MS. KEANE: In general.

01:39:09 8 THE COURT: All right. In general, I'm going to  
01:39:10 9 permit it. In general, my understanding of the question is,  
01:39:13 10 based on his experience, what's his general understanding as  
01:39:16 11 to why the FDA would sometimes strike out certain language?

01:39:19 12 MS. KEANE: Yes.

01:39:20 13 THE WITNESS: Yeah. So my understanding from my  
01:39:25 14 experience in regulatory affairs, having gone through labeling  
01:39:29 15 negotiations on multiple commercialized products, is that very  
01:39:34 16 commonly a Review Division who has purview for multiple  
01:39:39 17 products, so they are not just reviewing Amarin's Vascepa, but  
01:39:44 18 over time they have reviewed other products from other  
01:39:48 19 sponsors, and there's some attempt to try to keep the number,  
01:39:52 20 nature, phrasing of statements similar across products.

01:39:58 21 BY MS. KEANE:

01:39:59 22 Q And did you do anything to look into why this phasing in  
01:40:02 23 this particular circumstance was deleted?

01:40:05 24 A Yes. I -- knowing that the Review Division was  
01:40:10 25 responsible for reviewing a range of other lipid agents that

01:40:18 1 had -- you know, in which either lipid-lowering studies had  
01:40:23 2 been conducted, or cardiovascular outcome studies, I looked  
01:40:27 3 back through those labels, and that helped me understand that  
01:40:31 4 that language did not appear, for example, in the Lovaza  
01:40:37 5 label.

01:40:40 6 Q And were there any other labels that you reviewed in  
01:40:43 7 addition to the Lovaza label?

01:40:45 8 A Yes. I looked at a number of products that had reported  
01:40:50 9 out cardiovascular outcomes results in the diabetes class and  
01:40:58 10 also in the PCSK-9 inhibitor class.

01:41:04 11 Q And what did that review convey with respect to the  
01:41:13 12 chronic care population phraseology?

01:41:19 13 A So, for example, in the Lovaza label which had  
01:41:22 14 significant postmarketing experience, and was also indicated  
01:41:26 15 for use in a chronic use situation, that phrasing did not  
01:41:30 16 appear.

01:41:33 17 So we did not counter -- in the subsequent labeling  
01:41:37 18 round, we had that type of understanding and so it did not  
01:41:45 19 counterpropose it back to FDA.

01:41:47 20 Q And did that -- the review you did of additional labels,  
01:41:52 21 that informed your understanding as to why the language is not  
01:41:55 22 included in the final labeling?

01:41:57 23 A Yes, it did.

01:41:58 24 Q Okay. And so do you have an understanding as to why that  
01:42:03 25 language is not included in the final labeling?

01:42:06 1 A Yes, because it was not considered necessary or typical.

01:42:09 2 Q And when you say "not necessary or typical," what do you  
01:42:14 3 mean by that?

01:42:16 4 A The context of the development programs for placebo  
01:42:23 5 was -- were in chronic indications.

01:42:26 6 Q If we could turn to Plaintiffs' Exhibit 1185.

01:42:39 7 Do you recognize Plaintiffs' Exhibit 1185?

01:42:46 8 A Yes, I do.

01:42:47 9 Q And what is Plaintiffs' Exhibit 1185?

01:42:51 10 A It's a news release issued by the Food & Drug  
01:42:56 11 Administration on the date of approval -- of their approval of  
01:43:00 12 Vascepa for the expanded indication for cardiovascular risk  
01:43:03 13 reduction.

01:43:05 14 MS. KEANE: Your Honor, plaintiffs move to admit  
01:43:07 15 Plaintiffs' Exhibit 1185 into evidence.

01:43:10 16 MR. KLEIN: No objection.

01:43:10 17 THE COURT: 1185 is admitted.

01:43:10 18 (Plaintiffs' Exhibit 1185 received in  
01:43:13 19 evidence.)

01:43:13 19 BY MS. KEANE:

01:43:13 20 Q And do you know whether FDA typically issues a press  
01:43:17 21 release when it approves a new drug?

01:43:21 22 A It does not always issue a press release in my experience  
01:43:26 23 with the -- its approval of a new drug application or a  
01:43:30 24 supplemental new drug application.

01:43:32 25 Q And is it a frequent occurrence for FDA to issue a press

1 release with a new drug application?

2 A No. I would say that it's typically reserved for  
3 instances of first in class approvals or similar situations.

4 Q If we could pull up paragraphs -- the second and third  
5 paragraphs of the press release.

6 FDA states in the press release,

7 "The FDA recognizes that there is a need for  
8 additional medical treatments for cardiovascular  
9 disease."

10 Do you see that?

11 A Yes.

12 Q And then it goes on to state,

13 "Today's approval will give patients with  
14 elevated triglycerides and other important risk  
15 factors, including heart disease, stroke, and  
16 diabetes, an adjunctive treatment option that can  
17 help decrease their risk of cardiovascular events."

18 Do you see that?

19 A Yes.

20 Q What was Amarin's reaction to this press release?

21 A So we were not aware of FDA's intent to issue a press  
22 release until quite late in the process. We had plans for our  
23 own press release.

24 Obviously, as a small public company, and given the  
25 materiality, we were pleased. It's -- some of those



01:44:51 1 statements are consistent with what occurred early on in the  
01:44:54 2 review clock in terms of granting Vascepa priority review for  
01:44:59 3 this indication, which is also reflective of the un-met  
01:45:02 4 medical need and the need for additional therapies in this  
01:45:05 5 disease area.

01:45:07 6 Q And generally how have the results of REDUCE-IT been  
01:45:11 7 received?

01:45:11 8 A They've been received quickly, and I think with much  
01:45:18 9 acclamation. Some clinicians have considered it, you know,  
01:45:28 10 the most significant advance since statin therapy, others  
01:45:33 11 considered it practice changing.

01:45:35 12 And just speaking to a situation which is somewhat  
01:45:38 13 atypical, when the results, even prior to FDA approval, had  
01:45:44 14 already been embraced by a number -- and adopted by a number  
01:45:49 15 of national or international medical societies in terms of  
01:45:54 16 identifying icosapent ethyl as a promising therapy for the --  
01:46:01 17 as an add-on to statin therapy and cardiovascular risk  
01:46:04 18 reduction.

01:46:05 19 Q And what additional groups are you referring to?

01:46:08 20 A Amongst them are the American Diabetes Association, the  
01:46:14 21 National Lipid Association, the European Society of  
01:46:17 22 Cardiology, the European Atherosclerosis Society, and others.

01:46:23 23 MS. KEANE: Thank you, Dr. Ketchum. I have no  
01:46:25 24 further questions at this time.

01:46:38 25 THE COURT: Mr. Klein, do you need a few moments

01:46:40 1 to set up?

01:46:41 2 MR. KLEIN: Just a minute. We'll hand out  
01:46:43 3 binders, but I think I can do it pretty quickly.

01:46:51 4 May she approach the witness?

01:46:53 5 THE COURT: Yes.

01:47:07 6 MR. KLEIN: Your Honor, as technical matter, I'm  
01:47:10 7 going to be using slides. What I've done in advance to try to  
01:47:13 8 speed things along is I put snapshots and slides to go along.

01:47:17 9 Do you want a copy of it?

01:47:19 10 THE COURT: I don't need a copy. Thank you.

01:47:20 11 MR. KLEIN: Okay.

01:47:21 12 THE COURT: As long as the slide -- well, we'll  
01:47:21 13 take a look at the slide, but on the slide do you reference a  
01:47:26 14 particular exhibit number?

01:47:27 15 MR. KLEIN: I do.

01:47:28 16 THE COURT: Thank you.

01:47:30 17 MR. KLEIN: And one other housekeeping. Unlike  
01:47:33 18 plaintiff's counsel, what I intend to do is introduce all the  
01:47:36 19 exhibits I use at the end because I think it would be quicker,  
01:47:40 20 if that's okay.

01:47:41 21 THE COURT: Well, usually I think it's  
01:47:43 22 introduced as it goes along because of foundational issues.  
01:47:46 23 But if you believe there's not going to be any objections such  
01:47:49 24 that you don't have to worry about foundation, I'm fine with  
01:47:52 25 the approach of introducing all of the exhibits at the end.

01:47:55 1 MR. KLEIN: Okay. I mean, it's up to you.

01:47:56 2 THE COURT: In fact, there may even be a  
01:47:58 3 stipulation that the exhibits you want to offer are all  
01:48:01 4 admitted.

01:48:02 5 MR. KLEIN: I don't think there were any  
01:48:04 6 objections outstanding, but, you know, if something comes up,  
01:48:09 7 you're, obviously, free to object.

01:48:11 8 MS. KEANE: Yeah, Your Honor, I think there's  
01:48:12 9 just a couple of remaining issues. I think, in general, we  
01:48:15 10 don't have any remaining objections, because there are a few.  
01:48:18 11 And obviously we reserve the right, depending on how it is  
01:48:22 12 used with the witness, to object on foundation grounds.

01:48:24 13 THE COURT: So my concern, if you refer  
01:48:27 14 extensively to an exhibit, and you don't offer it for  
01:48:29 15 admission, and there's an objection at the end, and I sustain  
01:48:33 16 the objection, you would have wasted your time, and I would  
01:48:36 17 have to strike the testimony relating to that particular  
01:48:40 18 exhibit.

01:48:40 19 MR. KLEIN: I would say that's probably pretty  
01:48:42 20 unlikely, but I can --

01:48:43 21 THE COURT: You're pretty optimistic.

01:48:45 22 MR. KLEIN: Well, we exchanged objections in  
01:48:47 23 advance, so, yeah.

01:48:47 24 THE COURT: We'll proceed that way if you think  
01:48:49 25 that's more efficient.

01:48:50 1 MR. KLEIN: If there's an issue that comes up,  
01:48:52 2 we can raise it at the time.

01:48:59 3 CROSS-EXAMINATION

01:48:59 4 BY MR. KLEIN:

01:48:59 5 Q Good afternoon, Dr. Ketchum.

01:49:01 6 A Good afternoon.

01:49:02 7 Q You and I haven't met, right?

01:49:03 8 A That's correct.

01:49:04 9 Q My name is Charles Klein. I represent the defendants in  
01:49:07 10 this case.

01:49:10 11 You were designated as a corporate representative  
01:49:15 12 for Amarin during discovery under Federal Rule of Civil  
01:49:19 13 Procedure 30(b)(6), right?

01:49:21 14 A Yes, I was.

01:49:22 15 Q Okay. Let's go to -- and you probably heard the  
01:49:26 16 colloquy. What I'm going to be doing is, for the most part,  
01:49:29 17 putting snapshots on screen just because I think it will move  
01:49:32 18 things along. You obviously have a binder in front of you if  
01:49:36 19 you need it.

01:49:37 20 DX 1809, do you recognize this as the Notice of  
01:49:42 21 Deposition that defendants served?

01:49:45 22 A I -- I can see that it's a Notice of Deposition.

01:49:54 23 Q Okay. You may not recall the specific notice, but you  
01:50:00 24 recall a Notice of Deposition was served, and there were a  
01:50:03 25 number of topics on which you were designated to testify?

01:50:07 1 A Yes.

01:50:07 2 Q Okay. And I'm not going to go through all of them, but I  
01:50:11 3 just want to cover a few just so, for the record, we have the  
01:50:14 4 context for your 30(b)(6) testimony.

01:50:19 5 So, topic 12 was Amarin's methods, actions, steps  
01:50:23 6 taken, the rationale to differentiate Vascepa from Lovaza. Do  
01:50:28 7 you remember that?

01:50:28 8 A Yes.

01:50:29 9 Q By the way, you said Lo-vais-a. I don't know if that's  
01:50:32 10 the proper terminology. I've been calling it Lo-vau-sa for  
01:50:36 11 years -- or is it to-mait-o to-maut-o?

01:50:39 12 A Lo-vais-a is the correct pronunciation.

01:50:40 13 Q Okay. I'll try to remember that.

01:50:42 14 If we go to -- this is the same exhibit, DX 1809.  
01:50:47 15 I'll try to remember to call out the demonstrative as well.  
01:50:50 16 It's DDX 2.2.

01:50:52 17 Another topic concerned Amarin's presentations to  
01:50:56 18 investors. Do you remember that?

01:50:57 19 A Yes.

01:50:58 20 Q Then on DDX 2.3, Amarin's clinical programs for Vascepa.  
01:51:05 21 Do you remember that?

01:51:06 22 A Yes.

01:51:07 23 Q And then topic 32, this is DDX 2.4, was Amarin's  
01:51:13 24 assessment, impressions, and reliance on the JELIS clinical  
01:51:18 25 trial in their own clinical program for Vascepa and in

01:51:21 1 communications with FDA regarding Vascepa. Do you remember  
01:51:24 2 that?

01:51:24 3 A Yes.

01:51:25 4 Q All right. We move to the next exhibit, and this exhibit  
01:51:31 5 is DX 2255, and I'm -- for the record, I'm on DDX 2.5.

01:51:42 6 On direct you spent some time discussing Amarin's  
01:51:46 7 MARINE, ANCHOR, and REDUCE-IT clinical studies, right?

01:51:50 8 A Yes.

01:51:51 9 Q Okay. And you're obviously proud of those studies,  
01:51:54 10 right?

01:51:54 11 A Yes.

01:51:55 12 Q Okay. And those studies resulted in two FDA approved  
01:51:59 13 indications?

01:51:59 14 A Yes, they did.

01:52:00 15 Q And Amarin's reward for these successful clinical studies  
01:52:05 16 and new indications was a period of regulatory exclusivity,  
01:52:10 17 right?

01:52:11 18 Let me rephrase because I know you're still waiting  
01:52:14 19 on the second one.

01:52:15 20 For the first indication, you received regulatory  
01:52:15 21 exclusivity in return for the successful clinical trial and  
01:52:23 22 the severe hypertriglyceridemia indication, correct?

01:52:26 23 A Yes, with some delay.

01:52:26 24 Q Right.

01:52:27 25 A As reflected in the dating on this document.

01:52:29 1 Q Right. Yeah. And I'll a talk about that.

01:52:32 2 And then with regard to the new indication, Amarin  
01:52:35 3 is going to be applying for additional regulatory exclusivity,  
01:52:39 4 correct?

01:52:40 5 A Amarin will be entitled to additional exclusivity on the  
01:52:45 6 basis of having undertaken work, additional clinical work  
01:52:49 7 deemed to be essential for reviewing and approving an expanded  
01:52:53 8 indication for an additional use.

01:52:56 9 Q Right. And regulatory exclusivity means that FDA won't  
01:53:01 10 approve any generic product for some particular period, right?

01:53:05 11 A Yes, and its intent is to acknowledge that the sponsor,  
01:53:10 12 in arriving at that expanded indication has exerted a certain  
01:53:16 13 amount of time, energy, and financial wherewithal to get to  
01:53:20 14 that point.

01:53:20 15 Q Exactly. It's, in essence, a reward for the time and  
01:53:24 16 money you spent on the clinical trial, correct?

01:53:28 17 A It's -- it's to acknowledge and to allow the sponsor to  
01:53:36 18 have the opportunity to, you know, basically, you know,  
01:53:45 19 commercialize that expanded indication and continue to be have  
01:53:50 20 incentives to continue to develop, you know, other therapies  
01:53:50 21 for other unmet medical needs which is a timely and --

01:54:07 22 So I was just saying that exclusivity is a period of  
01:54:13 23 time that's an acknowledgement of the sponsor's resources that  
01:54:19 24 its deployed in the direction of that expanded indication  
01:54:23 25 because it's not always a successful endeavor.

01:54:29 1 It's very commonly all of that time, energy, and  
01:54:32 2 effort is spent without -- and the whole intent is to  
01:54:36 3 encourage innovation of therapies that can meet unmet medical  
01:54:42 4 needs, and that's just an inherently risky process.

01:54:45 5 Q Understood. And these periods of regulatory exclusivity  
01:54:49 6 are very important to companies like yours that's going  
01:54:53 7 through the effort in running clinical trials, right?

01:54:55 8 A I'm sorry, could you repeat the question again?

01:54:58 9 Q Sure. These periods of exclusivity, regulatory  
01:55:01 10 exclusivity, is very important to a company like your company  
01:55:05 11 that is undertaking the expense of a clinical trial, right?

01:55:08 12 A Yes. It's a very important consideration.

01:55:10 13 Q Right. It's designed, as I think you put it, to  
01:55:13 14 incentivize companies like Amarin to go ahead and spend the  
01:55:17 15 money on the clinical trial because you know that, if it's  
01:55:20 16 successful, you'll get a period exclusivity, right?

01:55:23 17 A And because many times it's not successful, and so we  
01:55:27 18 can't just focus on the situations where it is successful  
01:55:31 19 because sponsors are continually doing trials that don't  
01:55:35 20 succeed and that they never see the benefit of that level of  
01:55:40 21 effort.

01:55:45 22 Q Right. Right.

01:55:46 23 The MARINE study supported the original indication,  
01:55:49 24 and I think you even called it the MARINE indication on  
01:55:52 25 direct, right?



01:55:52 1 A That's correct.

01:55:53 2 Q And so on the screen is DX 2255. This is a press release  
01:56:01 3 from Amarin from May 31st, 2016, right?

01:56:05 4 A That's correct.

01:56:06 5 Q And here Amarin is announcing that the FDA has determined  
01:56:13 6 that Vascepa capsules are eligible for five years, new  
01:56:19 7 chemical entity, marketing exclusivity, pursuant to the  
01:56:22 8 Hatch-Waxman amendments, right?

01:56:24 9 A Yes. That's what that press release says.

01:56:26 10 Q And Amarin did in fact receive five years of new chemical  
01:56:31 11 entity exclusivity for the MARINE indication, right?

01:56:34 12 A Yes, it did, as reflected here.

01:56:36 13 Q Okay. Now, as you said, there was some delay. Initially  
01:56:40 14 FDA did not award the NCE, the new chemical entity  
01:56:46 15 exclusivity, right?

01:56:47 16 A Yes. It was not coincident with the date of FDA approval  
01:56:53 17 on July 26th, 2012.

01:56:54 18 Q Right. There was some litigation with FDA, and  
01:56:58 19 eventually it was resolved, and you got the NCE exclusivity  
01:57:05 20 right?

01:57:05 21 A Yes.

01:57:05 22 Q If we go to DDX 2.6, this press release says,  
01:57:13 23 "NC exclusivity for Vascepa runs from its  
01:57:15 24 date of FDA approval on July 26, 2012, and extends  
01:57:17 25 until July 26, 2017. The statutory 30-month stay

01:57:23 1 triggered by patent litigation following generic  
01:57:26 2 applications. Submissions permitted on July 26,  
01:57:29 3 2016, would expire on January 26, 2020,  
01:57:32 4 seven-and-a-half years from FDA approval."

01:57:37 5 Do you see that?

01:57:37 6 A Yes, I see that statement.

01:57:38 7 Q Okay. And you understand then under -- the way this  
01:57:44 8 five-year new chemical entity exclusivity works, the generics  
01:57:49 9 could not even file an application until four years into that  
01:57:53 10 period?

01:57:53 11 A Yes, I understand that.

01:57:54 12 Q Okay. And then the defendants' here obviously filed  
01:57:56 13 their applications, right? You knew that happened, right?

01:58:00 14 A Yes, I don't know exactly what date, but I do know that  
01:58:03 15 they've been filed.

01:58:03 16 Q But understand that after, after the defendants filed  
01:58:07 17 their applications Amarin brought suit and then there was an  
01:58:11 18 automatic 30-month stay that was instituted?

01:58:15 19 A Yes, I'm aware of that.

01:58:16 20 Q Okay. So the total amount of exclusivity plus the  
01:58:21 21 30-month stay totals seven-and-a-half years, right?

01:58:25 22 A Yes, it does.

01:58:26 23 Q Right. And so Amarin received seven-and-a-half years of  
01:58:30 24 regulatory exclusivity which means it was free from generic  
01:58:35 25 competition for that entire period, correct?

01:58:38 1 A Yes.

01:58:39 2 Q And Amarin got this exclusivity because FDA eventually  
01:58:46 3 determined that Vascepa is a new chemical entity; is that  
01:58:50 4 right?

01:58:50 5 A Yes.

01:58:50 6 Q And Vascepa is purified EPA, correct?

01:58:54 7 A Vascepa is an ethyl ester form of highly purified EPA.

01:58:59 8 Q Right. I mean, that's the chemical entity essentially?

01:59:02 9 A Icosapent ethyl.

01:59:05 10 Q Right. Amarin did not invent purified EPA though, right?

01:59:10 11 A I don't totally agree with that statement. Amarin is the  
01:59:18 12 owner of the NDA which describes all of the chemistry  
01:59:24 13 manufacturing controls of the particular ethyl ester form, a  
01:59:30 14 specific highly purified form of EPA, that is comprised in  
01:59:35 15 Vascepa as icosapent ethyl.

01:59:38 16 Q Let me clarify the question.

01:59:39 17 Amarin was not the first company to come up with a  
01:59:43 18 purified EPA product. Do you agree with that?

01:59:46 19 A I agree with that.

01:59:47 20 Q Yeah.

01:59:48 21 A We --

01:59:49 22 Q Yeah.

01:59:49 23 A Just as an example, we discussed earlier the Epadel  
01:59:53 24 product --

01:59:53 25 Q Correct.

01:59:53 1 A In Japan.

01:59:54 2 Q And, in fact, there were EPA containing dietary  
02:00:02 3 supplements available for quite some time, right?

02:00:05 4 A Yes, there are a range of dietary supplements containing  
02:00:11 5 omega-3s like EPA.

02:00:13 6 Q And then the Japanese authorities approved Epadel in  
02:00:18 7 Japan which is a purified EPA product, right?

02:00:22 8 A Yes, Epadel was approved in Japan for specified uses.

02:00:26 9 Q And Amarin's seven-and-a-half years of regulatory  
02:00:29 10 exclusivity was not based on a finding that Amarin had  
02:00:33 11 invented purified EPA, right?

02:00:36 12 A It was based on it being classified as a new chemical  
02:00:40 13 entity.

02:00:41 14 Q And what that means is that Amarin was the first to get  
02:00:44 15 FDA approval of a purified EPA product, correct?

02:00:48 16 A Amarin was the first in -- to bring that type of product  
02:00:52 17 to the market in the United States.

02:00:53 18 Q Right. But just to be clear, the NCE exclusivity doesn't  
02:01:00 19 mean that you created and was the first to invent purified  
02:01:04 20 EPA, you were just the first to get FDA approval of a purified  
02:01:08 21 EPA product; is that fair?

02:01:10 22 A That's correct, and, in fact, our new drug application  
02:01:13 23 had some degree of reliance on nonclinical information from  
02:01:16 24 the Mochida product.

02:01:17 25 Q Right. And just --

02:01:18 1 A Which classified it as a 505(b)(2) NDA while still being  
02:01:23 2 an NCE.

02:01:24 3 Q I'll unpack that a little bit. Number one, Mochida is  
02:01:29 4 the manufacturer of Epadel, right?

02:01:31 5 A Yes.

02:01:31 6 Q Okay. And so you reference a 505(b)(2) product. What  
02:01:36 7 that means is that under the regulations you told FDA that you  
02:01:40 8 were going to rely on Mochida's Epadel's information in part  
02:01:44 9 to support your application, correct?

02:01:47 10 A Yes. That's correct.

02:01:48 11 Q Now, we talked about how Amarin will be entitled to  
02:01:56 12 another three years of exclusivity related to the REDUCE-IT  
02:02:00 13 indication, right?

02:02:00 14 A Yes.

02:02:01 15 Q And what that means is that there won't be generic  
02:02:06 16 competition in terms of generic products that had the  
02:02:09 17 REDUCE-IT indication in their label for at least three years  
02:02:12 18 regardless of patents, correct?

02:02:14 19 A That's correct.

02:02:16 20 Q And that, too, is a regulatory incentive and a reward for  
02:02:27 21 Amarin to go ahead and conduct studies like the REDUCE-IT  
02:02:31 22 study, right?

02:02:32 23 A Yes, that took a decade plus and approximately  
02:02:35 24 \$300 million.

02:02:36 25 Q And you understand that all this regulatory exclusivity,

1 the seven-and-a-half years for MARINE and the three years for  
2 REDUCE-IT, is totally independent of patent rights, correct?

3 A I'm not an intellectual property expert, but, yes, I  
4 understand the regulatory provisions.

5 Q Those are just two totally different types of  
6 exclusivity, right? Those are two different types of  
7 exclusivity.

8 A Yes. Regulatory exclusivity in terms of NCE and  
9 Hatch-Waxman for having conducted a clinical trial and getting  
10 three years is different from additional exclusivity that can  
11 be afforded through other mechanisms.

12 Q And you're not a patent law expert, I assume, right?

13 A I am not.

14 Q But you generally understand sometimes clinical trials  
15 can support a patent, and sometimes they can't, right?

16 A I -- that sounds like a reasonable statement.

17 Q Okay.

18 A Again, not being a patent lawyer.

19 Q All right. So let's take a look at the last paragraph on  
20 DDX 2.7. Here it says,

21 "'Amarin's goal is to protect the commercial  
22 potential of Vascepa to 2030,' stated John Theorow,  
23 president and chief executive officer of Amarin. NCE  
24 regulatory exclusivity complements multiple patents  
25 covering Vascepa with expiration dates in 2030."

02:04:01 1 Do you see that?

02:04:01 2 A I see that statement.

02:04:04 3 Q And so you understand that -- well, number one, you  
02:04:06 4 understand that seven-and-a-half years is about to expire in  
02:04:10 5 the next couple weeks, right?

02:04:11 6 A Yes, based on the date in that press release.

02:04:14 7 Q Okay. But Amarin is hoping that its patents, the patents  
02:04:17 8 at issue in this case, are going to continue to block generic  
02:04:21 9 competition all the way to 2030; is that right?

02:04:24 10 A Amarin's perspective is that those patents support  
02:04:28 11 coverage of Vascepa for a longer period of time.

02:04:31 12 Q And you generally understand -- and I promise I'm not  
02:04:36 13 going to ask you details about it, but you generally  
02:04:37 14 understand that defendants are contending that they don't  
02:04:39 15 infringe the patents and that they're obvious, right?

02:04:42 16 A I understand that at a high level, again, not being an  
02:04:46 17 intellectual property lawyer.

02:04:48 18 Q All right. Now, let's go to DDX 2.8, and this is a  
02:04:58 19 snapshot from Amarin's proposed findings of fact, and it's ECF  
02:05:03 20 number 331.

02:05:05 21 Here, I just -- it's really an orientation question,  
02:05:07 22 I'm not going to ask you details about the inventors, but do  
02:05:13 23 you understand that Amarin contends in this case that the  
02:05:16 24 inventors listed on the patents conceived of their claimed  
02:05:20 25 inventions on or by March 25th, 2008? Is that something you

02:05:25 1 understand?

02:05:26 2 A This is not a document that I'm familiar with.

02:05:29 3 Q Okay. I will represent to you that this is -- this is a  
02:05:33 4 document that was filed with the court by counsel. Okay? And  
02:05:37 5 so you're saying you've never seen it?

02:05:39 6 A I'm saying I don't recall seeing it, and I don't recall  
02:05:43 7 the content of this document.

02:05:46 8 Q Well, let's -- let's proceed this way then. I will  
02:05:50 9 represent to you that the contention in this case -- just to  
02:05:54 10 orient yourself with regard to some of my next questions, the  
02:05:58 11 contentions in this case is that the alleged inventors  
02:06:03 12 conceived of the claimed invention by March 25th, 2008.

02:06:07 13 Okay? Do you this that date in your mind?

02:06:09 14 A I see that date on that slide.

02:06:11 15 Q All right. Let's go to the next slide. This is DDX 2.9,  
02:06:22 16 and it references DX 1814.

02:06:27 17 Do you recognize DX 1814?

02:06:35 18 A I believe I've seen this document before.

02:06:38 19 Q Okay. And as we just discussed, Amarin asserts that its  
02:06:44 20 date of conception is March 25th, 2008. Do you remember that?

02:06:48 21 A I -- I'm sorry, were you citing a different date than is  
02:06:54 22 highlighted there?

02:06:55 23 Q Well, I'm citing the date that we just talked about from  
02:06:58 24 the attorney submission to the court. That was March 25th, do  
02:07:03 25 you remember that?



02:07:03 1 A I remember that from that slide.

02:07:05 2 Q And so this is -- I'm just orienting you vis-à-vis that  
02:07:09 3 date.

02:07:10 4 So this document is March 10th, right?

02:07:13 5 A The date on this document is March 10th.

02:07:15 6 Q Okay.

02:07:15 7 A Again, just for clarity, this is not a point in time when  
02:07:18 8 I'm at Amarin so -- I was not hired in until February of 2012.

02:07:24 9 Q Okay. And I understand that, but this is one of the  
02:07:27 10 documents you discussed during your deposition, right?

02:07:30 11 A Yes.

02:07:30 12 Q Okay.

02:07:31 13 A I did.

02:07:31 14 Q And this document is dated 15 days before the alleged  
02:07:34 15 conception date, right?

02:07:36 16 A Based on those two slides, it's 15 days in advance.

02:07:44 17 Q Okay. And you understand that this document -- it's an  
02:07:46 18 internal Amarin document, right?

02:07:47 19 A It appears to be so. That's my recollection that it was  
02:07:52 20 an internal Amarin document.

02:07:54 21 Q Okay. And it discusses the rationale and outline of the  
02:07:57 22 proposed development program for Vascepa, correct?

02:08:01 23 A Yes. It's for the icosapent ethyl program for  
02:08:07 24 hypertriglyceridemia.

02:08:10 25 Q Okay. Let's go DX 1814, page 2, it's DDX 2.10, and this

02:08:17 1 is the second page of the document if you're looking at a hard  
02:08:21 2 copy.

02:08:21 3 A Uh-huh.

02:08:22 4 Q It's the introduction.

02:08:29 5 And you see generally the introduction starts by  
02:08:32 6 discussing the state of the art as of the date of this  
02:08:36 7 document, March 10, 2008, right?

02:08:38 8 A It's providing some type of introductory background. I  
02:08:42 9 can't comment on the state of the art portion of that  
02:08:46 10 statement.

02:08:46 11 Q Okay. Well, what I highlighted says,

02:08:48 12 "Ethyl EPA capsules, Epadel, have been  
02:08:51 13 marketed by Mochida in Japan since 1991. The  
02:08:55 14 approved indications are hyperlipidemia,"  
02:08:59 15 and then it goes on. Do you see that?

02:09:01 16 A Yes, I do see that.

02:09:03 17 Q And you generally understand that Mochida had marketed  
02:09:07 18 Epadel as a purified EPA product since 1991; is that right?

02:09:10 19 A Yes, that's correct.

02:09:11 20 Q And the approved indication includes hyperlipidemia, you  
02:09:16 21 knew that, right?

02:09:16 22 A Yes.

02:09:17 23 Q And hyperlipidemia means an abnormally high concentration  
02:09:21 24 of fats or lipids in the blood?

02:09:23 25 A It connotes that medical terminology.

02:09:27 1 Q It includes high triglycerides, right?

02:09:32 2 A I can't recall specifically how the Japanese characterize  
02:09:37 3 hyperlipidemia, but the term can mean multiple lipid  
02:09:40 4 abnormalities.

02:09:41 5 Q And hyperlipidemia also includes very high levels of  
02:09:46 6 triglycerides, right?

02:09:47 7 A I don't know in the specific context that it's  
02:09:49 8 specifically encompassed.

02:09:50 9 Q The term hyper --

02:09:53 10 A It's such a broad term as phrased on this document that  
02:09:56 11 there might be other documents that might need to be consulted  
02:10:00 12 to confirm.

02:10:00 13 Q Generally speaking, the term hyperlipidemia would include  
02:10:05 14 very high triglyceride levels, right?

02:10:07 15 A I -- that's a very broad statement that I can't agree  
02:10:11 16 with.

02:10:12 17 Normally, it would be qualified by, as an example,  
02:10:16 18 hypercholesterolemia, as was studied in the JELIS study, means  
02:10:22 19 high total cholesterol.

02:10:24 20 Hyperlipidemia is such a broad term, it's unclear  
02:10:31 21 precisely what it means in this specific context on this page.

02:10:31 22 Q Okay. But you understand that the Epadel product was  
02:10:34 23 used to reduce triglyceride levels, right?

02:10:36 24 A I know it was used to reduce a number of lipids.

02:10:41 25 Q Including triglycerides?

02:10:43 1 A I know that there had been some level of work done to  
02:10:46 2 characterize its ability to lower triglycerides, but, again,  
02:10:51 3 this statement is in the context of an approved indication,  
02:10:54 4 and I think there are other documents, Japanese documents,  
02:10:57 5 that would have to be consulted to clarify the meaning of that  
02:11:00 6 term in that marketed territory.

02:11:02 7 Q All right. Sir, even putting aside the document for now,  
02:11:06 8 it's just a straightforward question. You understand that the  
02:11:09 9 Epadel product was used before 2008 to reduce triglycerides in  
02:11:14 10 patients, right?

02:11:15 11 A It -- it was used -- I can't comment on how it was used  
02:11:22 12 by Japanese physicians in that marketed territory. Quite  
02:11:26 13 possibly it was used by some physicians to address a  
02:11:31 14 hyperlipidemic abnormality that included the need to lower  
02:11:35 15 triglycerides.

02:11:36 16 Q Okay, sir. So have you read any of the studies involving  
02:11:40 17 ep --

02:11:40 18 A Yes, I have, very closely, and that's why I referred to  
02:11:44 19 the most significant of those studies is the JELIS study where  
02:11:47 20 specifically the patients, their primary lipid abnormality was  
02:11:55 21 hypercholesterolemia meaning high total cholesterol. That was  
02:11:58 22 by far the most extensive study conducted by Mochida, and  
02:12:00 23 those patients actually had very modest triglyceride level.

02:12:05 24 Q But you're also aware of studies, aside from JELIS, that  
02:12:08 25 used Epadel and showed that Epadel reduced triglycerides,

02:12:15 1 correct?

02:12:15 2 A There's some reports in the peer reviewed literature that  
02:12:20 3 show -- that showed some ability of Epadel to reduce  
02:12:23 4 triglycerides.

02:12:24 5 Just to clarify for the judge, I'm reacting to the  
02:12:27 6 specific words where it's in a marketed context, and I want to  
02:12:30 7 make sure that I'm accurate about how I'm characterizing  
02:12:35 8 hyperlipidemia.

02:12:36 9 Q Okay. I'm not sure what you mean by marketed context.  
02:12:36 10 I'm not --

02:12:39 11 A The highlighted portion on the slide.

02:12:40 12 Q Putting aside the document, I'm just asking you generally  
02:12:43 13 does it -- in even clinical studies, you understand that  
02:12:49 14 Epadel or -- that Epadel was used in studies discussing the  
02:12:55 15 prior art to reduce triglycerides in human patients, right?

02:13:00 16 A You're using -- you know, prior art. I'm not one of the  
02:13:05 17 inventors on the patent so I --

02:13:06 18 Q Okay.

02:13:07 19 A That's not a term that I use in my day-to-day, you know,  
02:13:12 20 R&D responsibilities.

02:13:14 21 Q Okay. Fair enough. We'll get back to that.

02:13:18 22 If we go to the next slide, DDX 2.11, it's just  
02:13:25 23 different highlighting, it says,

02:13:26 24 "The efficacy and safety of Ethyl EPA in  
02:13:30 25 Japan have been further supported by the publication

02:13:32 1 in *The Lancet* earlier this year of the JELIS study in  
02:13:36 2 which over 18,000 patients with hyperlipidemia were  
02:13:41 3 randomized to receive ethyl-EPA or placebo on  
02:13:45 4 background statin therapy."

02:13:47 5 Do you see that?

02:13:48 6 A Yes, I do.

02:13:49 7 Q And you understand that *The Lancet* is one of the most  
02:13:52 8 prestigious scientific journals, right?

02:13:54 9 A Yes, I do.

02:13:56 10 Q And you're familiar with the JELIS study, obviously,  
02:13:58 11 right?

02:13:58 12 A Yes.

02:13:58 13 Q Let's go on to the last sentence on DDX 2.12. It says,  
02:14:02 14 "After a mean follow-up of 4.6 years, there  
02:14:04 15 was a clinically and statistically significant  
02:14:08 16 19 percent reduction in the primary endpoint of major  
02:14:11 17 coronary events."

02:14:13 18 Do you see that?

02:14:13 19 A Yes, I do.

02:14:14 20 Q And that's what *The Lancet* reported, right?

02:14:16 21 A It did, and, again, in a patient population with high  
02:14:21 22 total cholesterol.

02:14:22 23 Q Okay. Let's go to DDX 2.13, which is page 2 of the  
02:14:30 24 document, and here it says,

02:14:31 25 "Ethyl EPA as a single agent is not approved

02:14:34 1 as a prescription medicine in any other markets, but  
02:14:37 2 a combination of esters of EPA and DHA are marketed  
02:14:42 3 in USA as Lovaza" -- I got it right -- "and in  
02:14:46 4 various European countries as Omacor."

02:14:49 5 That's a true statement, right?

02:14:54 6 A That is a true statement.

02:14:55 7 Q Okay. And so before March 2008, the FDA had approved  
02:15:00 8 Lovaza as a combination EPA-DHA product, right?

02:15:04 9 A Yes. It approved it in 2004 for Lovaza.

02:15:09 10 Q Right. And it was indicated for very high triglycerides,  
02:15:13 11 right?

02:15:13 12 A Yes, it was.

02:15:14 13 Q All right. Let me move on to another paragraph on  
02:15:18 14 page 2, this is DDX 2.14, and here it says,

02:15:22 15 "Amarin has been investigating the potential  
02:15:25 16 of Ethel EPA to treat Huntington's disease,  
02:15:31 17 depression, and schizophrenia."

02:15:31 18 Do you see that?

02:15:32 19 A Yes.

02:15:32 20 Q Okay. And I think you mentioned on direct that these  
02:15:35 21 investigations did not lead to a viable product, correct?

02:15:39 22 A I don't recall mentioning it previously, but you are  
02:15:43 23 correct that the prior development program in Huntington's  
02:15:47 24 disease by Amarin did not lead to an approved indication in  
02:15:52 25 any territory.

02:15:52 1 Q Okay. I might be thinking of the opening statement, but  
02:15:56 2 I remember it coming up earlier today.

02:15:56 3 In DDX 2.15 is page 7 of the document, and here it  
02:16:03 4 says,

02:16:03 5 "Amarin has not performed any clinical trials  
02:16:05 6 of ethyl-EPA in patients with dyslipidemia."

02:16:11 7 So you understand as of March of 2008, Amarin  
02:16:14 8 had not yet performed any clinical trials to assess whether  
02:16:19 9 purified EPA could reduce triglycerides, correct?

02:16:21 10 A Yes, and the sentence goes on to explain what it had  
02:16:25 11 studied.

02:16:26 12 Q Right. It's the Huntington's disease, depression, and  
02:16:29 13 schizophrenia, right?

02:16:32 14 A Yes, CNS disorders.

02:16:34 15 Q Okay. Let's go to the next slide which is DDX 2.16, and  
02:16:38 16 this is DX 1814 at page 10.

02:16:43 17 Here, the document -- it's the same document. It  
02:16:50 18 says,

02:16:50 19 "Extensive clinical data attest to the safety  
02:16:54 20 and efficacy of combinations of EPA-DHA as treatment  
02:16:58 21 of dyslipidemias," and then it says, "approval of  
02:17:01 22 Lovaza, 4 milligrams daily, by FDA for severe  
02:17:06 23 hypertriglyceridemia."

02:17:09 24 Do you see that?

02:17:11 25 A Yes, I do see that.



Q Okay. And -- all right. Let's go to the next slide, DDX 2.17, this is page 10 of the document.

And here Amarin talks about how,  
"In view of the extensive clinical experience with ultra pure EPA, and with EPA-DHA products, Amarin contends that only further limited clinical data are required to confirm the efficacy and safety of ethyl-EPA as a treatment of severe hypertriglyceridemia."

Do you see that?

A Yes, I see that statement in that section.

Q Okay. And so because there was a lot of data on Epanolone and purified EPA, and also a lot of data on Lovaza, Amarin just needed to confirm that purified EPA without DHA could be used for the same purpose as Lovaza, correct?

A I don't agree with that statement.

Q Okay. It says,  
"Further limited clinical data are required to confirm the efficacy and safety of ethyl-EPA as a treatment of severe hypertriglyceridemia."

How is that different from what --

A Well, what I'm -- what I'm saying is that there was -- by virtue of Lovaza, I would acknowledge that there was a regulatory precedent. That precedent pointed to that a single trial could suffice for severe hypertriglyceridemia.

02:18:50 1 I don't consider that confirmation, I consider that  
02:18:53 2 a separate development program that had its own safety and  
02:18:53 3 efficacy requirements in order to surpass that development  
02:18:58 4 hurdle. That's different from just confirming someone else's  
02:19:02 5 efforts.

02:19:02 6 Q All right. So it's one -- Amarin felt it could proceed  
02:19:06 7 with developing Vascepa for the Lovaza indication with limited  
02:19:10 8 clinical data, correct?

02:19:12 9 A Yes. The prior regulatory precedent of Lovaza would have  
02:19:17 10 given the Amarin team the confidence that a relatively compact  
02:19:23 11 development program could suffice for severe  
02:19:26 12 hypertriglyceridemia.

02:19:26 13 Q Okay. Let's go to DDX 2.18.

02:19:29 14 Here, I just highlighted a different sentence.

02:19:33 15 "Specifically data are required to confirm  
02:19:36 16 the magnitude of effect and the dose response  
02:19:39 17 relationship of ethyl-EPA in lowering triglyceride  
02:19:43 18 levels in patients with baseline levels above  
02:19:47 19 500 milligrams per deciliter."

02:19:49 20 Do you see that?

02:19:50 21 A I see that statement.

02:19:51 22 Q And so Amarin was looking for confirmation data to  
02:19:55 23 support the development program for Vascepa, right?

02:19:58 24 A So, again, the context of this document is an internal  
02:20:05 25 document. I'm not entirely clear who the authors intended to

02:20:11 1 be the audience for that internal document, but it's spelling  
02:20:15 2 out the rationale for a clinical development program.

02:20:18 3 Q You raise a good point. You're not aware of this  
02:20:21 4 document being tied to any of the inventors, right?

02:20:25 5 A I -- I am looking at the document. I don't see any names  
02:20:35 6 on the document.

02:20:38 7 Q Let's go to DDX 2.19. Here it says,  
02:20:42 8 "Amarin does not believe there's a need to  
02:20:44 9 conduct any additional pharmacokinetic drug  
02:20:48 10 interaction or other studies," right?

02:20:50 11 A I see those words.

02:20:55 12 Q Okay. Is that -- is that what you were referring to with  
02:20:58 13 the 505(b)(2), that you were going to rely on Mochida's -- I  
02:21:03 14 say you, that Amarin was going to rely on Mochida's data?

02:21:07 15 A No.

02:21:07 16 Q Okay.

02:21:08 17 A In fact -- so I guess what I'm saying is some elements of  
02:21:11 18 this document are aspirational. They predate the significant  
02:21:15 19 interactions with FDA which didn't occur until the pre-IND  
02:21:20 20 meeting later.

02:21:21 21 So this is an instance where the authors of this  
02:21:27 22 document are making a certain rationale and proposal that has  
02:21:31 23 not yet been vetted with FDA.

02:21:34 24 Fast forward over time, as reflected in the approved  
02:21:37 25 prescribing information for the MARINE indication, in fact

02:21:40 1 Amarin did need to conduct a series of drug drug interaction  
02:21:44 2 studies to -- for the original new drug application to be  
02:21:48 3 received for review.

02:21:49 4 Q Got it. Okay.

02:21:51 5 This was the initial -- one of the initial drug  
02:21:55 6 development internal documents, right, and you're saying, you,  
02:21:58 7 know things may not have worked out as planned as the  
02:22:02 8 regulatory process unfolded?

02:22:03 9 A I can't comment on initial and demarcate any period of  
02:22:12 10 time. This is a team that's been working on EPA for quite  
02:22:16 11 some years, and, yes, in a different context, in a CNS  
02:22:20 12 context, but they obviously had been steeped in EPA for some  
02:22:24 13 time.

02:22:24 14 Q Okay. Let's go to the next slide, still in same  
02:22:28 15 document, page 10, it's DX 1814, page 10. It's DDX 2.20.

02:22:34 16 And this internal document -- development document  
02:22:38 17 where we've been discussing cites some references, right?

02:22:42 18 A Yes, it does.

02:22:43 19 Q And two of the references that are cited are Lovaza and  
02:22:47 20 Yokoyama, right?

02:22:48 21 A Yes, that's correct.

02:22:49 22 Q And you understand Yokoyama is the JELIS article in *The*  
02:22:56 23 *Lancet*, right?

02:22:56 24 A Yes.

02:22:56 25 Q Okay. Let's go to the next slide, and this is another

02:23:10 1 document, it's -- there are actually two documents here, and  
02:23:15 2 I'll explain it in a moment. It's DX 1829, which is the  
02:23:20 3 document on the left, and then DX 2241 is the metadata for  
02:23:25 4 that document, and that's what's on the right, and the slide  
02:23:29 5 is DDX 2.21, and the document on the left --

02:23:34 6 A I'm sorry, could I --

02:23:35 7 Q Sure, sure.

02:23:36 8 A Could you explain what metadata means in this  
02:23:39 9 particular -- I'm just kind of familiar with the general term.

02:23:43 10 Q Okay. Let me back up a little bit.

02:23:45 11 So the document on the left you recognize, DX 1829,  
02:23:49 12 from your deposition, right?

02:23:51 13 A Yes.

02:23:51 14 Q Okay. The metadata is what was produced to us from  
02:23:56 15 Amarin that ties to this document that gives us some more  
02:24:00 16 information such as the date and the custodian whose files it  
02:24:05 17 came from. That's what metadata means.

02:24:08 18 Okay. And I'm including the metadata because I  
02:24:10 19 could not find a date on the document, so we looked at the  
02:24:13 20 metadata for the date.

02:24:15 21 And so I'll represent to you that the date of the  
02:24:19 22 document, according to the metadata, is March 20th, 2008.

02:24:24 23 Okay?

02:24:24 24 A Okay.

02:24:25 25 Q All right. We're still five days before the alleged date

02:24:30 1 of conception which, as you recall, was March 25th, 2008,  
02:24:34 2 right?

02:24:36 3 A Again, with that background on the March 20th date, yes,  
02:24:39 4 that would be five guys before.

02:24:41 5 Q Okay. If we go to DDX 2.22, I've highlighted the  
02:24:47 6 custodian of the document from the metadata, and this  
02:24:51 7 indicates that the document it came from Stewart Sedlack's  
02:24:56 8 files. Okay. You see that?

02:24:57 9 A I see that.

02:24:59 10 Q And he is a senior VP of corporate development, right?

02:25:03 11 A I was not with Amarin at this time, but that's my  
02:25:07 12 understanding is that was his functional role.

02:25:12 13 Q And I think you explained at the deposition that your  
02:25:15 14 understanding is that this document, DX 1829, is a business  
02:25:19 15 development document; is that right?

02:25:20 16 A That's my understanding.

02:25:22 17 Q And you understand that Mr. Sedlack is not one of  
02:25:28 18 inventors in this case, do you understand?

02:25:29 19 A Yes, I understand.

02:25:31 20 Q All right. Let's go to the next slide which is -- we're  
02:25:34 21 looking now at page 4 of DX 1829, and the slide is DDX 2.23.

02:25:42 22 You see the heading is Amarin's ARM101 for  
02:25:46 23 Triglyceride Lowering, that's the title?

02:25:49 24 A Yes, that's the title of that Section.

02:25:51 25 Q And you mentioned this earlier, but AMR 101 is the code

02:25:56 1 name for Vascepa, right?

02:25:57 2 A Yes.

02:25:58 3 Q And I highlighted a sentence that says,

02:26:00 4 "An identical drug, Epadel, ultra pure  
02:26:05 5 ethyl-EPA, has already been approved in Japan for  
02:26:08 6 this indication."

02:26:09 7 The indication referring to triglyceride  
02:26:11 8 lowering, right?

02:26:12 9 A I see those words.

02:26:15 10 Q And do you --

02:26:16 11 A And I was just going to say Stewart Sedlack is not a --  
02:26:21 12 was not an R&D scientist or a regulatory affairs professional,  
02:26:27 13 and so I can't speak to his precise choice of words within  
02:26:31 14 this document.

02:26:31 15 Q Okay. But does this refresh your recollection as to  
02:26:35 16 whether Epadel was approved for lowering triglycerides in  
02:26:41 17 Japan?

02:26:42 18 A As an R&D and regulatory affairs person, I'd prefer to be  
02:26:48 19 looking at the approved labeling in Japan as opposed to going  
02:26:52 20 from an internal Amarin document.

02:26:54 21 Q And Mr. Sedlack characterized Vascepa, or AMR 101, as  
02:27:01 22 identical to Epadel in this document, right?

02:27:06 23 A Yes, he did.

02:27:07 24 Q Let's go to the next slide which is just going down the  
02:27:10 25 page and over to the next page, it's DX 1829, pages 4 to 5,

02:27:15 1 DDX 2.24.

02:27:17 2 And here there's a header that says Lovaza Versus --  
02:27:20 3 I'll just call it Vascepa, okay? It says AMR 101, but for  
02:27:26 4 short I'll just call it Vascepa. Do you see that?

02:27:29 5 A Yes, I do.

02:27:30 6 Q Okay. And it says,

02:27:30 7 "It is clear from the data generated to date  
02:27:33 8 that both Lovaza, EPA-DHA, and Epadel EPA identical  
02:27:39 9 to Vascepa, are effective in lower triglycerides."

02:27:42 10 Do you see that?

02:27:42 11 A Yes, I can see those statements written in this document  
02:27:47 12 by that author.

02:27:48 13 Q But that was well-known as of March 2008, right?

02:27:51 14 A Identical is -- there's --

02:28:00 15 Q Let me rephrase. I'm not actually referring to  
02:28:03 16 identical.

02:28:03 17 It is well-known that both Lovaza and Epadel are  
02:28:09 18 effective in lowering triglycerides as of March 2008, right?

02:28:09 19 A I would say to differing degrees. Clearly one was  
02:28:13 20 approved for that use in the United States, and one was  
02:28:16 21 approved for use in a broader hyperlipidemic context within  
02:28:22 22 another territory, Japan.

02:28:24 23 Q Right. But Amarin certainly did not discover that  
02:28:27 24 purified EPA could lower triglycerides, right?

02:28:30 25 A Amarin -- so, I think it's important to point out that --



as I did in an different context, that there are differences in the way that Mochida conducted its studies in totally different patient population, different dietary backdrop.

We only have a certain level of understanding exactly how Mochida performed those studies. There's relatively little information in the peer reviewed literature. So I don't consider it having been established to the same degree.

And so I think there was some views, some rationale of being developed by certain Amarin authors of, you know, how to design and conduct a development program. But, they were in possession of other information from the CNS program that they'd worked on for many years, and so those weren't the only sources of information in terms of pointing to Lovaza or Epadel.

Q Sir, I think you varied from my question. Let me try to be more concise.

Are you disputing that it was clear from the data generated in March 2008 that both Lovaza and Epadel are effective in lowering triglycerides?

A It's the term effective. There's various standards required to establish effectiveness. So I'm using it in a registration context. So my view is that Lovaza had been proven to a greater degree than had Epadel.

Q But they --

02:30:18 1 A In a U.S. patient population context.

02:30:21 2 Q Okay. I'm not limiting my questions to the United  
02:30:24 3 States. Let's try to break it down a little bit.

02:30:26 4 The data generated by March 2008 clearly  
02:30:30 5 demonstrated that Epadel was effective in lowering  
02:30:34 6 triglycerides, correct?

02:30:36 7 A There was some body of evidence established by Mochida  
02:30:39 8 that Epadel could reduce triglycerides.

02:30:42 9 Q And Lovaza was FDA approved for lowering triglycerides at  
02:30:47 10 least in patients with very high triglycerides, right?

02:30:50 11 A Yes, as an adjunct to diet and with its particular other  
02:30:54 12 label considerations.

02:30:56 13 Q So Amarin didn't discover either of those two things.  
02:31:00 14 Can we agree on that?

02:31:02 15 A Amarin was not the first in the severe  
02:31:08 16 hypertriglyceridemia space. You know, I would acknowledge  
02:31:11 17 that. And Amarin -- EPA had been studied in other  
02:31:21 18 formulations previously, including by Amarin, in a different  
02:31:27 19 disease area.

02:31:28 20 Q And pure EPA was also studied in triglyceride-lowering --

02:31:35 21 A A form of purified EPA. Again, it's -- there are  
02:31:39 22 differences, different dosage form, different supply chain,  
02:31:44 23 different raw material suppliers. All of those are important.  
02:31:48 24 Not all so-called EPA products are the same from a chemistry  
02:31:54 25 manufacturing and control perspective.

Q Okay. Let's go to further down in this paragraph again we're on DX 1829, pages 4 to 5, and DDX 2.25.

Here is says,

"However, one differentiating feature is their respective effect on LDL levels. Lovaza treatment may result in elevations in LDL in some individuals, and such individuals should be monitored to ensure their LDLs do not increase excessively. Consequently, the FDA required this information be included in Lovaza's package insert. Conversely, Epadel treatment does not appear to have the same effect on LDL levels as supported by Mochida's studies on Epadel as well as independent studies."

Do you see that?

A I see those words.

Q Yes. Okay. So the phrase "Mochida's studies on Epadel as well as independent studies" is clearly referring to studies that were not conducted by Amarin, correct?

A Those would not have been -- I -- it seems to be constructed to be speaking about Epadel only so Amarin would not have conducted those studies.

Q And this Amarin document from March 20, 2008, says that Epadel treatment does not appear to have the same effect on LDL levels as Lovaza according to published studies conducted by others, correct?

02:33:35 1 A I'm sorry, which part of this are you referring to?

02:33:39 2 Q It's the conversely sentence, the last sentence that's  
02:33:43 3 highlighted.

02:33:44 4 A Uh-huh.

02:33:44 5 Q So this document from March 20th, 2008, says that,  
02:33:48 6 "Epadel treatment does not appear to have the  
02:33:50 7 same effect on LDL levels as supported by Mochida's  
02:33:55 8 studies on Epadel as well as independent studies."

02:33:59 9 Do you see that?

02:33:59 10 A Yes. I'm focused on the "does not appear."

02:34:02 11 Q Okay. All right.

02:34:03 12 A It's differentiated from the level of information that  
02:34:07 13 had been established in the phrasing within the prior  
02:34:10 14 sentences for Lovaza.

02:34:11 15 Q All right. Well, the next sentence on DDX 2.26 says,  
02:34:15 16 "Hence there's no reference to Epadel  
02:34:17 17 treatment causing LDL elevation in Epadel's packaging  
02:34:22 18 insert. Vascepa is also expected to have a better  
02:34:27 19 dosing regimen compared to Lovaza, 2 grams per day  
02:34:29 20 versus 1 gram per day."

02:34:31 21 Do you see that?

02:34:32 22 A I see those words.

02:34:33 23 Q Okay. You understand that the Epadel product -- are you  
02:34:38 24 familiar with the Epadel product label?

02:34:41 25 A I'm familiar with aspects of it, yes.

02:34:43 1 Q Okay. But you understand it does not contain a warning  
02:34:46 2 about LDL-C side effects like the warning in the Lovaza label,  
02:34:51 3 right?

02:34:51 4 A I haven't consulted the Epadel, you know, approved  
02:34:56 5 prescribing information recently.

02:34:57 6 Q But you have no reason to doubt the statement in here --

02:35:00 7 A I have a priori reason to doubt this statement.

02:35:04 8 Q Okay. Fair enough.

02:35:06 9 Let's go to the next slide, same document, DX 1829,  
02:35:11 10 page 5, DDX 2.27.

02:35:13 11 The title here is AMR 101 or Vascepa in Triglyceride  
02:35:19 12 Lowering Next Steps. Do you see that?

02:35:20 13 A Yes, I see that heading.

02:35:22 14 Q And it says,

02:35:23 15 "Amarin is currently preparing a submission  
02:35:25 16 for the FDA to obtain guidance regarding the  
02:35:28 17 development program required for approval of AMR 101  
02:35:32 18 in triglyceride lowering. At this time Amarin  
02:35:35 19 expects that an outcome study will not be required  
02:35:39 20 given the clinical evidence already available to  
02:35:43 21 date."

02:35:44 22 Do you see that?

02:35:44 23 A I see that phrasing.

02:35:46 24 Q Okay. And, again, you understand that the clinical  
02:35:48 25 evidence already available to date is referring to the

02:35:52 1 clinical evidence other than -- outside the context of Amarin,  
02:35:57 2 right?

02:35:57 3 A I don't necessarily interpret it that way.

02:36:02 4 Q Okay.

02:36:02 5 A It's vague enough that it could encompass some of the  
02:36:06 6 Amarin work.

02:36:06 7 Q All right. Let's go to the next slide, which is  
02:36:13 8 DDX 2.28, and this is DX 1829, page 6.

02:36:15 9 This section is Scientific Support, A Review of Key  
02:36:19 10 Publications. Do you see that?

02:36:21 11 A Yes, I see that section.

02:36:23 12 Q And then it says hypertriglyceridemia and cardiovascular  
02:36:27 13 disease?

02:36:28 14 A Yes.

02:36:28 15 Q And then underneath it says,

02:36:31 16 "Several studies have explored and supported  
02:36:33 17 the protective effect of omega-3 fatty acids of  
02:36:37 18 MARINE origin against serum lipids and cardiovascular  
02:36:43 19 disease including...."

02:36:44 20 Do you see that?

02:36:45 21 A I see that preface, yes.

02:36:47 22 Q Okay. And if we go to the next slide, and I promise I  
02:36:50 23 won't ask you to read it, but you can just generally see that  
02:36:53 24 where we left off before, there are four bullets with four  
02:36:57 25 discussions of literature dating before March 2, 2008. Can

02:37:04 1 you generally see that?

02:37:05 2 A Yes, I see those sections.

02:37:07 3 Q Okay. I'm going to zoom in now to the fourth one. This  
02:37:10 4 is DDX 2.30, and here it says,

02:37:14 5 "While data to date supports the positive  
02:37:17 6 effects of both EPA, Epadel/Vascepa and EPA-DHA  
02:37:25 7 (Lovaza) in lowering triglycerides, no clinical  
02:37:28 8 studies have been conducted directly comparing the  
02:37:30 9 efficacy of these treatments. However, a few studies  
02:37:33 10 have assessed the independent effects of EPA and DHA.  
02:37:37 11 One such study was described by Trevor Mori, et al.,  
02:37:40 12 in the *American Journal of Clinical Nutrition* in  
02:37:45 13 2000."

02:37:45 14 Do you see that?

02:37:46 15 A I see that statement.

02:37:49 16 Q Okay. And are you familiar with the Mori reference from  
02:37:51 17 2000?

02:37:51 18 A Yes, I've got that publication before.

02:37:55 19 Q All right. Let's take look at that, that's DX 1538. Do  
02:37:59 20 you recognize this as the Mori reference?

02:38:02 21 A Yes, I do.

02:38:03 22 Q And the objective --

02:38:05 23 MS. KEANE: Objection, Your Honor.

02:38:07 24 Dr. Ketchum is not here as an expert witness, he  
02:38:10 25 is here as a fact witness, and this is getting into substance

of expert testimony.

MR. KLEIN: I'm discussing the study that's in the document on which he was designated as a 30(b)(6) witness.

I'm not going to ask him to interpret the document, I'm just going to ask him what Mori reported according to its plain language.

THE COURT: Ms. Keane, was Dr. Ketchum designated as a 30(b)(6) witness on this particular topic?

MS. KEANE: He was designated as a 30(b)(6) witness. I don't believe he was designated on this document specifically.

MR. KLEIN: This document was addressed in his deposition, and this is a reference that's referred to in the document.

MS. KEANE: So I agree that he discussed the document during his deposition, that does not mean he was designated as a 30(b)(6) on this topic.

THE COURT: Well, if he already has been deposed on this issue, and counsel is representing that he's not going to go into any question requiring the expertise, then I'm going to overrule the objection.

The objection is he's not an expert and hasn't been designated as an expert on this topic. I'm overruling the objection. We'll see the specific question as we go along. If you believe there's basis to object, Ms. Keane, you



02:39:23 1 can object.

02:39:23 2 MS. KEANE: Okay. Thank you, Your Honor.

02:39:25 3 BY MR. KLEIN:

02:39:25 4 Q You understand, based on your familiarity with the Mori  
02:39:30 5 reference, that the objective of this study was to determine  
02:39:33 6 whether EPA or DHA acids have differential effects on the  
02:39:38 7 serum lipids?

02:39:39 8 A I see that stated objective within the publication.

02:39:43 9 Q Okay. And if we go to DDX 2.32, you understood that the  
02:39:48 10 design of this study was a double-blind, placebo-controlled  
02:39:55 11 trial of parallel design, right?

02:39:57 12 A Yes, but my understand is that's it's not within a  
02:39:57 13 registration context to differentiate it from some of the  
02:40:01 14 other studies that we've discussed.

02:40:04 15 Q A registration context? What do you mean?

02:40:06 16 A Yes. In terms of the level of rigor on certain terms  
02:40:11 17 like double-blind, placebo-controlled, can convey that they  
02:40:16 18 have a certain level of, you know, regulatory gravitas, and  
02:40:20 19 I'm saying that my understanding is that this is not a study  
02:40:23 20 in that type of category.

02:40:25 21 Q I see. So you're saying this isn't like an FDA study.

02:40:28 22 A This is not FDA reviewed --

02:40:28 23 Q Understood.

02:40:30 24 A -- designed in agreement with FDA to compare with the  
02:40:33 25 Lovaza or with the Vascepa studies.

02:40:36 1 Q But you understand that the EPA product at issue in Mori  
02:40:40 2 was 4 grams?

02:40:41 3 A I do. But I don't believe it's the same as Epadel, and  
02:40:46 4 I'm not entirely sure how it was formulated.

02:40:49 5 Q Okay. I didn't ask whether it was the same --

02:40:51 6 A I know, I'm just commenting as part of my perspectives on  
02:40:55 7 this study, I'm unaware of exactly how the EPA was  
02:40:59 8 administered in terms of a dosage form.

02:41:01 9 Q Understood, but, you know, because this is cross-examine,  
02:41:04 10 try to limit your answers to my question.

02:41:06 11 You also understand that what Mori reported was that  
02:41:10 12 LDL cholesterol increased significantly with DHA but not with  
02:41:15 13 EPA, right?

02:41:16 14 A I see the P values and the level of nonsignificance.

02:41:23 15 It's a small study, and I think there are other  
02:41:28 16 sections of the paper that put into context the views on the  
02:41:34 17 relative effects of EPA and DHA on other lipid parameters.

02:41:38 18 Q I didn't ask about those other effects.

02:41:40 19 Let's go back to the document that we were looking  
02:41:43 20 at, DX 1829, page 11. There's an appendix devoted to the Mori  
02:41:49 21 reference, do you see that?

02:41:51 22 A Yes.

02:41:53 23 Q Okay. And it's called Appendix 4, EPA versus DHA, Mori,  
02:41:58 24 et al., do you see that?

02:41:59 25 A Yes, I see that.

02:42:01 1 Q And the top of the page says,

02:42:02 2 "There have been relatively few studies aimed  
02:42:04 3 at determining whether EPA and DHA have differing  
02:42:07 4 effects on serum lipids and lipoproteins in humans.  
02:42:12 5 However, one such study was described by Trevor  
02:42:16 6 Mori."

02:42:16 7 Right? I think we talked about that moment ago.

02:42:18 8 A Yes.

02:42:19 9 Q And what we didn't look at is the chart. You see there's  
02:42:22 10 a chart in this document that repeats this statement that we  
02:42:26 11 just looked at,

02:42:26 12 "In Mori, serum LDL increased significantly  
02:42:30 13 with DHA by 8 percent, but not with EPA,  
02:42:34 14 3.5 percent."

02:42:35 15 Right?

02:42:35 16 A Yes, I see those words.

02:42:37 17 Q Okay. And that comment is consistent with what we just  
02:42:40 18 looked at in Mori, right?

02:42:46 19 A Those particular statements are consistent between those  
02:42:50 20 two sections.

02:42:50 21 Q Right. Let's blow up the bottom of the chart a little  
02:42:55 22 bit. Here it says,

02:42:56 23 "DHA was also associated with an increase in  
02:42:59 24 LDL cholesterol."

02:43:02 25 Do you see that?

02:43:03 1 A I see that.

02:43:03 2 Q Okay. And these observations by Amarin were obviously  
02:43:07 3 based on the publically available Mori reference which was  
02:43:11 4 published back in 2000, correct?

02:43:12 5 A That would have been one of the elements in the  
02:43:20 6 scientific literature available to Amarin.

02:43:21 7 Q All right. Let's go back to this busy page that  
02:43:27 8 identified four references. Do you remember that?

02:43:29 9 A Yes.

02:43:30 10 Q Okay. And I'm going to now zero in on the third one.  
02:43:34 11 This is DDX 2.36. And here it says,

02:43:39 12 "In 2007, the investigators of a large scale  
02:43:43 13 study, the Japan EPA lipid intervention study JELIS,  
02:43:47 14 reported in *The Lancet*, that the frequency of major  
02:43:49 15 coronary events is reduced with EPA, 19 percent, P  
02:43:56 16 equals 0.01, given in combination with statin versus  
02:43:59 17 treatment with statin alone."

02:44:01 18 Do you see that?

02:44:02 19 A Yes, I see that.

02:44:07 20 Q Let's turn the page 10 of DX 1829, and you see there's an  
02:44:11 21 appendix devoted to EPA in the JELIS study?

02:44:17 22 A Yes, I see that.

02:44:19 23 Q And the last sentence of this paragraph says JELIS was  
02:44:23 24 set up to test the hypothesis that long-term use of EPA is  
02:44:28 25 effective in reduction of major coronary events in Japanese

02:44:35 1 hypercholesteremia patients given statins, right?

02:44:38 2 A Yes, I see that sentence.

02:44:39 3 Q Okay. And if we go further on, page 10 of DX 1829, it  
02:44:44 4 says,

02:44:44 5 "In summary, the JELIS study showed that the  
02:44:48 6 frequency of major coronary events is reduced with  
02:44:51 7 EPA 19 percent compared to controls," right?

02:44:55 8 A Yes.

02:44:55 9 Q And that was in fact an accurate description of the JELIS  
02:44:59 10 study, right?

02:45:00 11 A It was in terms of the administration of that dosage form  
02:45:04 12 in that patient population.

02:45:06 13 Q Okay. Now, we spent some time going through two  
02:45:09 14 documents. Both of these documents are before March 25th,  
02:45:13 15 2008, right?

02:45:14 16 A Yes, they are.

02:45:17 17 Q Okay. So I want to just recap what we went through.

02:45:20 18 Number one, Amarin knew from public sources that  
02:45:29 19 before 2008 it was known that purified EPA was approved in  
02:45:35 20 Japan to reduce triglycerides, right?

02:45:36 21 A So that's the hyperlipidemia aspect that I was mentioning  
02:45:41 22 that I'm just not personally familiar with the details of the  
02:45:46 23 Japanese label to confirm whether it's approved specifically  
02:45:51 24 to reduce triglycerides.

02:45:53 25 The hyperlipidemia term is different than

02:45:58 1 hypertriglyceridemia, but I'm allowing for the fact that there  
02:46:00 2 had been some work conducted to show that there was some  
02:46:03 3 reduction in triglycerides.

02:46:04 4 Q Let me go back a couple slides here to 2.32. Going back  
02:46:09 5 to the Mori reference. We didn't talk about this, but if you  
02:46:14 6 see the second snapshot, it says,

02:46:18 7 "After adjusting for baseline values  
02:46:22 8 triacy" -- it's another word for triglycerides,  
02:46:23 9 right? "Decreased significantly by 18.4 percent with  
02:46:27 10 EPA."

02:46:31 11 Do you see that?

02:46:33 12 A Triacylglycerols --

02:46:37 13 Q Is that another word for triglyceride?

02:46:39 14 A Well, it would depend on the methodology described in the  
02:46:42 15 paper and how the compounds were extracted from the blood.  
02:46:46 16 There might be some differences, actually.

02:46:49 17 Q Okay. Do you understand, based on your reading of Mori,  
02:46:53 18 that Mori reported that triglycerides were reduced by EPA?

02:47:00 19 A I'm sorry, I'm trying to find the Mori publication again.

02:47:04 20 Q Well, let's -- let's go back to this demonstrative I had  
02:47:10 21 here.

02:47:10 22 Let's take out Epadel. Pure EPA was -- well, no,  
02:47:16 23 Epadel was approved in Japan, right? You understand that.

02:47:19 24 A Yes.

02:47:19 25 Q Okay.

02:47:20 1 A Epadel was approved in Japan for a number of indications.

02:47:24 2 Q Okay. And it included triglycerides. You understand  
02:47:29 3 that, right?

02:47:29 4 A I'm --

02:47:31 5 Q Yeah.

02:47:32 6 A -- accepting what you're saying with my comment that I'm  
02:47:36 7 not sitting here with the approved prescribing information for  
02:47:40 8 Japan.

02:47:41 9 Q And Epadel did not warn about LDL-C increases, correct?

02:47:45 10 A Again, I'll accept it on the same basis that I'm not  
02:47:49 11 sitting here with the approved prescribing information in  
02:47:51 12 Japan.

02:47:52 13 Q Okay. Lovaza was approved in the US to treat severe  
02:47:56 14 hypertriglyceridemia, right?

02:47:58 15 A That's correct.

02:47:59 16 Q Lovaza warned about LDL-C increases, right?

02:48:02 17 A Yes, in addition to reflecting that the triglyceride  
02:48:06 18 reductions were associated with those LDL-C increases.

02:48:09 19 Q And Mori used 4 grams, 96 percent pure EPA, to reduce  
02:48:15 20 triglycerides, right?

02:48:17 21 A Of some -- I don't know the purity. I don't know the  
02:48:22 22 formulation. I don't know the sources for the formulation  
02:48:28 23 used in Mori.

02:48:37 24 Q Do you have any reason to dispute that Mori used 4 grams,  
02:48:40 25 96 percent pure EPA to reduce triglycerides?

02:48:45 1 A If it's extracted from the publication, and you're saying  
02:48:54 2 that, then I have no reason to not believe that.

02:48:59 3 Q Okay. Mori found LDL-C increased significantly with DHA  
02:49:04 4 and not EPA. You remember that, right?

02:49:07 5 A I just want to say that we're citing Mori a fair amount,  
02:49:25 6 but at the end, the conclusion of the article is that DHA --

02:49:29 7 Q No, I --

02:49:29 8 A -- may be more favorable.

02:49:31 9 Q -- understand there are other comments in Mori with  
02:49:33 10 regard to DHA. You know, if your counsel wants to bring them  
02:49:37 11 up, that's fine. I'm sure it's going to come up with the  
02:49:40 12 experts. But I'm just asking you about that one statement.

02:49:43 13 Mori found LDL-C increased significantly with DHA  
02:49:47 14 but not EPA. That comes from the paper, right?

02:49:58 15 So I'll go back to the chart we just looked at.  
02:50:01 16 This is from the document.

02:50:05 17 "Serum LDL increased significantly with DHA  
02:50:09 18 but not with EPA."

02:50:09 19 Do you see that?

02:50:09 20 A Yes, I see that.

02:50:11 21 Q I'm not misleading you.

02:50:13 22 A I see that.

02:50:14 23 Q Okay. And,

02:50:15 24 "JELIS showed the frequency of major coronary  
02:50:19 25 events is reduced with EPA 19 percent compared to



02:50:22 1 controls."

02:50:23 2 That was known as of March 2008, right?

02:50:25 3 A Statin controls without a placebo.

02:50:29 4 Q Right.

02:50:37 5 Now, have you read Amarin's pretrial brief in this  
02:50:41 6 case?

02:50:44 7 A I don't believe that I have.

02:50:46 8 Q Okay. All right. Well, I'll represent to you that this  
02:50:51 9 page, page 19, comes from Amarin's pretrial brief which is ECF  
02:50:56 10 327, and here, Amarin says,

02:50:58 11 "Even in patients with modestly elevated  
02:51:01 12 triglycerides, the prior art did not teach that EPA  
02:51:04 13 would avoid rises in LDL-C."

02:51:07 14 Do you see that?

02:51:07 15 A I see that sentence.

02:51:09 16 Q All right. And then it goes on to say,

02:51:12 17 "To the contrary, defendants' own reference,  
02:51:15 18 Mori 2000, reported that EPA, like DHA, increased  
02:51:18 19 LDL-C," it goes on.

02:51:20 20 Do you see that?

02:51:21 21 A I see that next sentence.

02:51:23 22 Q Okay. And then Amarin says,

02:51:26 23 "The prior art as a whole reflected the  
02:51:29 24 understanding that both DHA and EPA raised LDL-C even  
02:51:34 25 in mildly hyperlipidemic patients."

02:51:37 1 Do you see that?

02:51:38 2 MS. KEANE: Your Honor, I like to renew the  
02:51:41 3 objection about asking Dr. Ketchum about subject matters that  
02:51:41 4 are expert testimony.

02:51:41 5 Counsel is now asking him about discussions  
02:51:41 6 about the prior art. Dr. Ketchum is not here to testify as an  
02:51:49 7 expert.

02:51:49 8 THE COURT: There hasn't been a question asked  
02:51:51 9 yet. He's just reading what Amarin's statement is. I'm going  
02:51:54 10 to at least give counsel the benefit of the doubt. Have him  
02:51:58 11 ask a question. If you have an objection, then you have your  
02:52:01 12 objection.

02:52:01 13 BY MR. KLEIN:

02:52:02 14 Q These not the types of statements that Amarin told  
02:52:05 15 investors back in the 2008 to 2010 time frame, right?

02:52:09 16 A I was not present at Amarin. I can't comment with that  
02:52:14 17 general statement.

02:52:14 18 Q Okay. Fair enough. We'll look at some of the documents  
02:52:18 19 that were used in your deposition.

02:52:20 20 This is DX 1800, and the slide is DX 2.41.

02:52:25 21 Do you remember this document called Next Generation  
02:52:27 22 Lipid Modification in Cardiovascular Disease?

02:52:30 23 A Yes, I've seen this document before.

02:52:32 24 Q Okay. It's dated March 2010, right?

02:52:35 25 A It is.

02:52:35 1 Q Okay. You understand this was a document for investors?

02:52:41 2 A Yes. By virtue of the second page that has a forward  
02:52:47 3 looking statement. My understanding is this was directed to  
02:52:49 4 an investor audience.

02:52:51 5 Q Okay. And given that this was a presentation for  
02:52:54 6 potential investors, Amarin did the best job it could, to your  
02:52:58 7 understanding, to make sure the representations in the  
02:53:00 8 presentation were accurate, right?

02:53:02 9 A Yes. I'm not aware of the authors, but, yes, that would  
02:53:06 10 have been their operating principle.

02:53:08 11 Q Yeah, that's -- generally speaking, that's Amarin's  
02:53:12 12 policy is they want to be candid and forthcoming with  
02:53:15 13 investors, right?

02:53:16 14 A Amarin wants to be truthful in its representation of  
02:53:20 15 information, yes.

02:53:21 16 Q Okay. Let's go to DX 1800, page 3, and the slide is  
02:53:27 17 DDX 2.42.

02:53:28 18 Do you see this heading, Amarin Positioned For Near  
02:53:31 19 Term Success?

02:53:31 20 A Yes.

02:53:32 21 Q And here Amarin's talking to investors about its lead  
02:53:37 22 product which is AMR 101 Vascepa for elevated triglycerides,  
02:53:43 23 right?

02:53:43 24 A Yes.

02:53:44 25 Q Okay. And if we go to the slide 10, DX 1800, page 10,

02:53:48 1 and the demonstrative is DDX 2.43, the slide says there's  
02:53:54 2 clear a differentiation between Vascepa and Lovaza, right?

02:53:58 3 A Yes, that's the slide heading.

02:54:02 4 Q Okay. And Vascepa, like Lovaza, was being developed for  
02:54:06 5 patients with triglycerides above 500 at this time, right?

02:54:10 6 A Lovaza had been approved for about six years at this  
02:54:15 7 point, five, six years.

02:54:16 8 Q Yeah. No, my question really -- and it may not have been  
02:54:19 9 asked very well. Amarin was developing Vascepa for the same  
02:54:25 10 indication that had been approved for Lovaza, that is, very  
02:54:28 11 high triglycerides, correct?

02:54:29 12 A It was pursuing the same indication, yes.

02:54:33 13 Q Right. And you see there's a line, LDL effect?

02:54:37 14 A Yes.

02:54:37 15 Q And Amarin told the investors that for Lovaza the LDL  
02:54:43 16 effect is it elevates LDL-C, right?

02:54:47 17 A Yes.

02:54:47 18 Q And then Amarin told the investors that for LDL effect  
02:54:50 19 for Vascepa there was no DHA induced elevation, right?

02:54:55 20 A I see those words. I'm -- I was not an author of this  
02:55:01 21 document so I'm not entirely sure exactly what was factored  
02:55:05 22 into that statement.

02:55:07 23 Q Understood. And I understand you're testifying as a  
02:55:12 24 corporate witness here, but you do understand that these  
02:55:16 25 statements came from what was taught in the prior art, right?

02:55:20 1 Or in the literature, I'll say the literature.

02:55:25 2 A I -- I wouldn't say that it was exclusively in other  
02:55:34 3 people's work. So in March 2010, Amarin had -- even before  
02:55:41 4 embarking on the cardiovascular trials mentioned here, the  
02:55:45 5 lipid-lowering trials, it had conducted its own work in a  
02:55:50 6 range of disease areas.

02:55:52 7 Q Okay. Let's see what the document says. If we go to  
02:55:55 8 DX 1800, page 12, this is DDX 2.44, do you see there's a slide  
02:56:01 9 devoted to the title Multiple Studies Demonstrate That DHA  
02:56:07 10 Raises LDL-C?

02:56:07 11 A Yes, I see that heading.

02:56:09 12 Q And, to the best of your knowledge, Amarin thought this  
02:56:12 13 was a truthful statement that it was making to the investors,  
02:56:16 14 right?

02:56:18 15 A Yes.

02:56:18 16 Q Okay. And you can see all the references are dated  
02:56:23 17 before 2008, right?

02:56:24 18 A The publications at the left of that are all before 2008.

02:56:31 19 Q And then if we go to DX 1800, slide 13, and this is  
02:56:38 20 DDX 2.45, there's a slide devoted to the point that multiple  
02:56:42 21 studies demonstrate that EPA is LDL neutral, right?

02:56:47 22 A Yes, that's the content of that slide.

02:56:50 23 Q And this was a truthful statement by Amarin to its  
02:56:53 24 investors, correct?

02:56:55 25 A Yes. Multiple studies, that allows for not all studies.

02:57:02 1 Q Okay. And there are six studies listed in the slide?

02:57:07 2 A There are six studies listed on that slide.

02:57:10 3 Q Okay. And that was done in case the investors wanted to  
02:57:14 4 confirm the statement, presumably, right?

02:57:17 5 A Yes. It was intended as a resource.

02:57:19 6 Q Okay. And all -- none of these studies were Amarin  
02:57:23 7 studies, correct?

02:57:26 8 A Looking at the authors, I do not believe that any of  
02:57:32 9 those were.

02:57:32 10 Q And they're all dated before 2008?

02:57:36 11 A They are all dated before 2008.

02:57:38 12 Q Okay. And the slide lists the Mori reference we talked  
02:57:42 13 about, right?

02:57:42 14 A I don't know whether Mori published multiple. I -- I  
02:57:53 15 assume that it's the same publication we were speaking about  
02:57:56 16 previously.

02:57:57 17 Q Okay. You see there's --

02:57:58 18 A There's not a more specific annotation, that's what I'm  
02:58:01 19 referring to.

02:58:02 20 Q Okay. And you see it says Change in LDL on the right for  
02:58:05 21 Mori?

02:58:05 22 A Yes.

02:58:06 23 Q And it says zero?

02:58:08 24 A I see the zero.

02:58:10 25 Q And that's truthful because Mori said there was no

02:58:13 1 statistically significant increase in LDL, right?

02:58:19 2 A Again, the authors report it, and this presumably is a  
02:58:27 3 faithful reporting of what the authors reported.

02:58:30 4 Q And then there's the reference Kurabayashi from 2000 is  
02:58:35 5 on the chart as well, right?

02:58:36 6 A Yes.

02:58:37 7 Q That --

02:58:39 8 A I can't tell on that slide whether that's -- whether  
02:58:42 9 there's a sign in front of the --

02:58:46 10 Q What do you mean by a sign?

02:58:47 11 A Like a negative sign or a plus sign.

02:58:50 12 Q Oh, in the change in LDL?

02:58:50 13 A Yes.

02:58:52 14 Q That's what I was actually just going to look at. It's  
02:58:55 15 negative 5.88 percent.

02:58:57 16 A Okay.

02:58:58 17 Q Okay. So that would have been a truthful representation  
02:59:01 18 of Kurabayashi reference by Amarin to the investors, right?

02:59:06 19 A It would have -- I, again, was not author, I was not at  
02:59:08 20 Amarin at the time, but Amarin would expect that the people  
02:59:11 21 constructing this slide, that they would have consulted the  
02:59:15 22 reference and pulled the numbers and done a crosschecking to  
02:59:18 23 make sure that there was an accurate pulling from the  
02:59:20 24 reference.

02:59:21 25 Q And so Amarin told investors back in March 2010 that

02:59:26 1 Kurabayashi, Mori, and other references, demonstrated EPA is  
02:59:31 2 LDL neutral, right?

02:59:33 3 A Yes. Those slides are saying that there are multiple  
02:59:38 4 studies in the peer reviewed literature that support those  
02:59:44 5 points. That's not to say that they're exhaustive and that  
02:59:48 6 all studies demonstrate that.

02:59:50 7 Q Right. I didn't ask you that, but --

02:59:52 8 A Uh-huh.

02:59:53 9 Q And you said support those points, what you mean is the  
02:59:56 10 point that multiple studies demonstrate that EPA is LDL  
03:00:01 11 neutral, correct?

03:00:01 12 A Yes.

03:00:02 13 Q Okay. Let's go to another exhibit, DX 2104, and this,  
03:00:09 14 for the record, is DDX 2.46.

03:00:12 15 Do you recognize this as an Amarin citizen petition  
03:00:17 16 filed on June 24th, 2014, with the FDA?

03:00:23 17 A Yes. I see -- I see that it's a document from Amarin  
03:00:29 18 with that date.

03:00:30 19 Q And if we go to DDX 2.47, it's the last page, you signed  
03:00:38 20 this citizen petition, right?

03:00:40 21 A Yes, I did.

03:00:40 22 Q And so you were making representations on behalf of  
03:00:43 23 Amarin to the FDA in this document, right?

03:00:46 24 A Yes, I was.

03:00:49 25 Q And FDA regulates Amarin, right?



03:00:51 1 A Yes, FDA does.

03:00:53 2 Q So you obviously did the best job you could to ensure  
03:00:56 3 that your representations to the FDA were truthful and  
03:01:00 4 accurate, right?

03:01:01 5 A Yes, that's correct.

03:01:03 6 Q Let's go to DDX 2.48, and this DX 2104, page 1.

03:01:09 7 In this citizen petition, generally speaking, I'm  
03:01:13 8 not going to ask you the details about the merits of the  
03:01:15 9 citizen petition, but you were generally requesting that FDA  
03:01:19 10 impose sort of bioequivalence testing requirements on any ANDA  
03:01:26 11 that lists Vascepa as the reference listed drug, right?

03:01:30 12 A Yes.

03:01:31 13 Q Let's go to DX 2104, page 9, and this is DDX 2.49.

03:01:38 14 And you see -- I highlighted a sentence here that  
03:01:41 15 says,

03:01:41 16 "Additionally, in a double-blind,  
03:01:44 17 placebo-controlled trial comparing the biological  
03:01:47 18 effects of EPA and DHA in hyperlipidemic men, doses  
03:01:52 19 of 4 grams per day of EPA or DHA administered for six  
03:01:56 20 weeks each significantly lowered triglyceride  
03:01:59 21 levels."

03:01:59 22 Do you see that?

03:02:00 23 A Yes. I see that sentence.

03:02:03 24 Q Okay. Sounds familiar, right?

03:02:05 25 A Yes.

03:02:06 1 Q Okay. The footnote is the Mori reference we were talking  
03:02:10 2 about, right?

03:02:10 3 A Yes.

03:02:11 4 Q Okay. And so Mori did report that 4 grams per day of EPA  
03:02:18 5 significantly lowered triglyceride levels, correct?

03:02:22 6 A Yes, and, again, in the context of what's being phrased  
03:02:29 7 in this document, not to the level of registration quality  
03:02:36 8 study.

03:02:37 9 Q Right. No, and I'm not asking you whether it was FDA  
03:02:39 10 type study.

03:02:40 11 A Uh-huh.

03:02:41 12 Q Okay. DDX 2.51, I just highlighted the next sentence  
03:02:45 13 which says,

03:02:45 14 "The data from that study support, however,  
03:02:48 15 that EPA and DHA have differential effects on other  
03:02:53 16 well-studied lipid parameters such as LDL-C and  
03:02:57 17 HDL-C."

03:02:57 18 Do you see that?

03:02:58 19 A Yes.

03:02:59 20 Q Okay. And so you told the FDA that Mori supports the  
03:03:02 21 finding that EPA and DHA have differential effects on LDL-C,  
03:03:10 22 correct?

03:03:10 23 A In the context of there being additional requirements for  
03:03:15 24 ANDA filers because of some of these observations.

03:03:19 25 Q Right. What you were doing --

03:03:21 1 A It's a different context than other contexts that we've  
03:03:25 2 discussed in the Mori article.

03:03:27 3 Q Fair enough. What you're -- you're citing this in the  
03:03:30 4 citizen petition because you're arguing to the FDA that DHA in  
03:03:34 5 essence would be an impurity in a generic product, right?

03:03:39 6 A Yes, and it that could lead to different types of lipid  
03:03:43 7 effects.

03:03:43 8 Q Right. And so you're telling the FDA EPA and DHA have  
03:03:47 9 differential effects, and therefore, if generics had DHA, then  
03:03:53 10 it's not bioequivalent, right?

03:03:53 11 A Or that could be extended to other impurity profiles.

03:03:58 12 Q Fair enough. And, as you recall, the Mori reference  
03:04:02 13 concluded that LDL-C increased significantly with DHA but not  
03:04:06 14 with EPA, right?

03:04:08 15 A That was one of the statements in that publication.

03:04:12 16 Q Right. And so one of the reasons DHA could be an  
03:04:18 17 impurity in a generic would be that it could have the side  
03:04:23 18 effect of LDL-C. That's what you're telling the FDA, right?

03:04:30 19 A We're telling the FDA that a highly purified EPA product  
03:04:36 20 that does not exclude any other impurities could lead to  
03:04:40 21 different biological effects, and it's citing this as one  
03:04:44 22 example of that, but it's not be an exhaustive, it was done as  
03:04:49 23 a representative example. It could have had, you know,  
03:04:52 24 another omega-3 or omega-6 or other impurity in there.

03:04:56 25 Q Okay. The only reference you cited was the Mori

03:04:59 1 reference for this proposition, right?

03:05:01 2 A Yes.

03:05:01 3 Q Mori said, vis-à-vis differential effects, among other  
03:05:05 4 things, DHA can increase LDL-C, but EPA will not, correct?

03:05:12 5 A It said that in that study that there were differential  
03:05:16 6 effects between those two.

03:05:18 7 Q Yeah, and found that DHA increased LDL-C, but EPA did  
03:05:22 8 not, right?

03:05:22 9 A In that single, rather small, nonregistration study.

03:05:32 10 Q Now, we talked about the JELIS study a few moments ago.  
03:05:38 11 Do you remember that?

03:05:38 12 THE COURT: Mr. Klein, are you about to move to  
03:05:40 13 another exhibit?

03:05:41 14 MR. KLEIN: Yes. Do you want to take a break?

03:05:42 15 THE COURT: I think this is a good point for us  
03:05:45 16 to take our afternoon break of about 15 minutes.

03:23:43 17 (A recess was taken.)

03:23:43 18 THE COURT: Please be seated.

03:23:50 19 Mr. Klein?

03:23:51 20 MR. KLEIN: Thank you.

03:23:51 21 BY MR. KLEIN:

03:23:52 22 Q Let's move on to the next document which is DX 1816, and  
03:23:56 23 the slide is DDX 2.52.

03:23:59 24 Do you recognize -- you're familiar with this  
03:24:06 25 document, sir?

03:24:06 1 A Yes.

03:24:07 2 Q This may have been one of the ones you look at on direct.  
03:24:14 3 Honestly I can't recall because of lot of them look the same.  
03:24:18 4 Is this one of the ones you testified to on direct?

03:24:20 5 A This is basically the intermediate between some of the  
03:24:24 6 other communications that were in a prior exhibit.

03:24:28 7 So previously shared the actual request from Amarin,  
03:24:33 8 the conduct at the meeting, this is some time after the  
03:24:40 9 meeting was granted, Amarin sharing the package, the  
03:24:47 10 premeeting package with FDA.

03:24:50 11 Q I see. Okay. And so this is letter -- just to be clear,  
03:24:52 12 this is letter from Amarin's US agent to the FDA dated  
03:24:56 13 June 16th, 2008, right?

03:24:58 14 A Yes, that's correct.

03:25:00 15 Q Okay. And do you understand that Amarin didn't file its  
03:25:04 16 first patent application until February 2009, so after this  
03:25:08 17 document?

03:25:09 18 A I'm not an inventor on any of those patents. I don't --

03:25:13 19 Q That's fair.

03:25:15 20 A It's not my domain of responsibility.

03:25:17 21 Q Fair enough.

03:25:18 22 A I hear the date that you said.

03:25:22 23 Q Generally speaking, this is an information package for  
03:25:26 24 FDA concerning Amarin's investigation on a new drug  
03:25:28 25 application for Vascepa, right?

03:25:30 1 A Yes, it's the pre-IND meeting package.

03:25:33 2 Q Okay. In essence, what that means it's Amarin's applying  
03:25:37 3 to FDA to start clinical testing, right?

03:25:42 4 A So this is a consultative meeting before the IND has been  
03:25:47 5 submitted and opened which would enable the subsequent  
03:25:47 6 clinical development.

03:25:55 7 Q And Amarin obviously wanted to be candid and truthful in  
03:25:59 8 all of its representations to the FDA, right?

03:26:01 9 A Yes.

03:26:02 10 Q Let's go to DX 1816, page 80, which is DDX 2.53.

03:26:08 11 Do you see this is section 11.4.2, Published Studies  
03:26:13 12 JELIS Trial, right?

03:26:15 13 A Yes.

03:26:16 14 Q Okay. And I'm not sure I asked you this question, but  
03:26:19 15 just so the record is clear, Amarin had nothing to do with the  
03:26:22 16 JELIS trial, right?

03:26:23 17 A Correct.

03:26:24 18 Q JELIS was sponsored by Mochida, the maker of Epedel?

03:26:30 19 A That's correct.

03:26:31 20 Q Okay. But Amarin was relying on the JELIS trial to  
03:26:35 21 support its investigational new drug application, right?

03:26:39 22 A Relying on is perhaps too strong a word. It was  
03:26:44 23 mentioning it within -- along with many other pieces of work  
03:26:47 24 in this same meeting package.

03:26:50 25 Q Okay. This is one of the published studies that Amarin

03:26:52 1 is reporting on in its application to the FDA, right?

03:26:55 2 A This is not an application.

03:26:56 3 Q I mean --

03:26:57 4 A This is a --

03:26:58 5 Q -- in the letter.

03:26:59 6 A This is a meeting package to form the basis for a  
03:27:02 7 dialogue around what would be required for the development of  
03:27:05 8 Vascepa.

03:27:06 9 Q I stand corrected. But this is -- Amarin's discussing  
03:27:09 10 the JELIS trial as one of the published studies to be  
03:27:13 11 discussed with FDA, right?

03:27:16 12 A It's certainly one of the trials that is mentioned within  
03:27:22 13 that background package.

03:27:24 14 Q Let's go to DX 1816 page 81, and this is DDX 2.54.

03:27:32 15 And Amarin is explaining to the FDA -- you can  
03:27:35 16 generally see the paragraphs talking about JELIS, right?

03:27:35 17 A Yes.

03:27:39 18 Q And Amarin's -- if you look at what I highlighted, Amarin  
03:27:42 19 is explaining to FDA that each capsule in the JELIS trial  
03:27:46 20 contained 98 percent purified EPA, right?

03:27:49 21 A I see those words.

03:27:51 22 Q And then Amarin says,

03:27:53 23 "Although the study was not double-blind, all  
03:27:54 24 endpoints and severe adverse events were reviewed and  
03:27:58 25 adjudicated in a blinded fashion by an endpoint,

03:28:02 1 committee," right?

03:28:03 2 A Yes, with that sentence highlighted by you.

03:28:06 3 Q And, by the way, Amarin did not invent -- was not the  
03:28:12 4 first party to create a 98 percent pure EPA product, right?

03:28:18 5 A I -- again, I'm not a chemistry manufacturing controls  
03:28:31 6 formulation development expert. I'm not -- I'm seeing the  
03:28:36 7 words on the page.

03:28:37 8 I do know that Epadel had different purities over  
03:28:42 9 time and across its own commercialization and development  
03:28:46 10 pathway, and that there were earlier iterations that were  
03:28:51 11 lesser percentages of purity.

03:28:53 12 Q Given that this was a representation to the FDA, is it  
03:28:56 13 reasonable for Court to assume that Mochida created a 98  
03:29:02 14 percent pure EPA product before March 2008?

03:29:10 15 A This -- this information, if it's pulled accurately from  
03:29:14 16 the source documentation, which I believe it would be, is  
03:29:17 17 speaking to Mochida representing that it had a 98 percent  
03:29:24 18 purified EPA formulation at the time -- you know, prior to the  
03:29:28 19 time that this briefing book was submitted.

03:29:30 20 Q And what Amarin is saying here is that even though JELIS  
03:29:36 21 was not double-blind, Amarin's speaking positively about the  
03:29:41 22 JELIS study and saying it was adjudicated in a blinded fashion  
03:29:46 23 by an endpoint committee, correct?

03:29:48 24 A Yes, that is a positive aspect of the JELIS trial.

03:29:52 25 Q And if we go to DX 1816, page 83, which is DDX 2.55,



03:29:59 1 there is a section here called 11.5.2, Rationale For  
03:30:04 2 Development of Ethyl-EPA For the Treatment of Severe  
03:30:08 3 Hypertriglyceridemia. Do you see that?

03:30:11 4 A Yes, I do.

03:30:11 5 Q So this is explaining the rationale for developing  
03:30:15 6 Vascepa, right?

03:30:15 7 A Yes, for that indication.

03:30:16 8 Q Okay. And let's go to the last paragraph of this  
03:30:18 9 section, it's DX 1816, page 85, DDX 2.56, and this says,

03:30:25 10 "Currently Lovaza is the only FDA-approved  
03:30:27 11 product derived from fish oil that is available for  
03:30:32 12 prescription to patients with severe  
03:30:34 13 hypertriglyceridemia."

03:30:36 14 Do you see that?

03:30:36 15 A Yes, I see that statement.

03:30:37 16 Q And then it says,

03:30:39 17 "A formulation of highly purified Ethyl-EPA  
03:30:42 18 may have some advantages over Lovaza."

03:30:45 19 Right? That part actually wasn't highlighted.

03:30:47 20 A Uh-huh. I see that sentence.

03:30:49 21 Q Then it says,

03:30:50 22 "Lovaza is known to cause rises in LDL  
03:30:54 23 cholesterol particularly in patients with marked  
03:30:57 24 hypertriglyceridemia at baseline," right?

03:31:00 25 A Yes.

03:31:03 1 Q And then Amarin tells the FDA,

03:31:16 2 "In clinical studies performed with Ethyl-EPA  
03:31:19 3 to date, including the 18,000 patient JELIS study,  
03:31:23 4 there is no evidence of a significant rise in LDL  
03:31:27 5 cholesterol," correct?

03:31:28 6 A Yes, that's what this sentence says.

03:31:30 7 Q Okay. And as of this point in time, Amarin had not  
03:31:34 8 conducted any of its own trials to assess whether EPA  
03:31:38 9 increases LDL-C, correct?

03:31:42 10 A Amarin had not yet conducted any clinical studies in  
03:31:46 11 their cardiovascular development program, but it had spent  
03:31:51 12 years conducting studies in other disease areas where lipid  
03:31:57 13 panels might have been taken.

03:31:59 14 Q Okay. But this statement to the FDA that,

03:32:01 15 "In clinical studies performed with EPA to  
03:32:04 16 date, there's no evidence of a significant rise in  
03:32:07 17 LDL cholesterol,"

03:32:09 18 that's referring to JELIS and Epadel studies and studies like  
03:32:13 19 Mori, not Amarin studies, correct?

03:32:17 20 A That specific sentence isn't annotated with footnoted --  
03:32:23 21 so certainly speaking to JELIS, it's not clear exactly the  
03:32:31 22 expansiveness to which it's referring.

03:32:33 23 Q Okay. But you're pretty confident that this is not  
03:32:35 24 referring to any Amarin study testing whether EPA causes a  
03:32:39 25 significant rise in LDL cholesterol, that was not something

03:32:43 1 that Amarin had looked into as of this date, right?

03:32:46 2 A I'm was not an author of this document so I cannot state  
03:32:49 3 that definitively.

03:32:51 4 Q Okay.

03:32:52 5 A The authors might very well have had access to other  
03:32:55 6 information.

03:32:56 7 Q The authors certainly didn't say they were relying on  
03:32:59 8 Amarin data, right?

03:33:00 9 A This is not the type of a document where you use terms  
03:33:04 10 like relying upon, that sounds more like intellectual property  
03:33:09 11 terminology.

03:33:10 12 Q Okay. Let's go to the next document. These are actually  
03:33:12 13 two documents, but they're related. DX 1837 is on the left,  
03:33:16 14 and DX 1836 is on the right, and I started on the left because  
03:33:20 15 this is a letter from you to the FDA, February 27th, 2014,  
03:33:25 16 right?

03:33:25 17 A Yes, that's correct.

03:33:27 18 Q And that's the cover letter to DX 1836, correct?

03:33:35 19 A That is the cover letter to that other exhibit, 1836.

03:33:40 20 Q Okay. And DX 1836 is the formal dispute resolution  
03:33:44 21 request that you talked about on direct, right?

03:33:46 22 A That's correct.

03:33:47 23 Q And so just for some context, Amarin before this had  
03:33:53 24 conducted the ANCHOR study, right?

03:33:55 25 A Yes.

03:33:56 1 Q And the purpose of the ANCHOR study was to support a  
03:34:00 2 separate indication for cardiovascular effects, right?

03:34:03 3 A No, it was for a separate lipid focused indication in  
03:34:10 4 patients who were on a statin with triglycerides in the range  
03:34:15 5 of 200 to 499, to reduce triglycerides and lipids and  
03:34:20 6 lipoproteins inflammatory markers.

03:34:20 7 Q Fair enough. And we'll talk about that in a little bit.  
03:34:22 8 But the FDA rejected it, right?

03:34:24 9 A The --

03:34:27 10 Q The baseline --

03:34:28 11 A Precise regulatory terminology --

03:34:28 12 (Simultaneous indecipherable conversation.)

03:34:36 13 MR. KLEIN: Sorry. Go ahead. Go ahead.

03:34:38 14 THE WITNESS: So FDA first rescinded the special  
03:34:41 15 protocol assessment without acting on the application. That  
03:34:48 16 enabled us to go through these various disputes -- dispute and  
03:34:52 17 appeals which took quite some time.

03:34:58 18 I believe the complete response letter was not  
03:35:00 19 issued until sometime in 2015. So there was quite a delay.

03:35:05 20 The action date was supposed to be in December  
03:35:10 21 of 2013. So you can see that this process took some time.

03:35:13 22 BY MR. KLEIN:

03:35:13 23 Q Right. And I'm just setting up the context for this  
03:35:16 24 formal dispute resolution request. This is in the context of  
03:35:19 25 FDA -- you disputing FDA's findings with regard to the ANCHOR

03:35:24 1 study, correct?

03:35:25 2 A Yes, we were disputing their rescission of the SPA.

03:35:29 3 Q And you obviously tried to be truthful in this document  
03:35:33 4 as it was submitted to FDA, correct?

03:35:35 5 A Correct.

03:35:35 6 Q Let's go to DX 1836, page 6, which is DDX 2.58.

03:35:42 7 This is a section that talks about the ANCHOR SNDA,  
03:35:47 8 right?

03:35:47 9 A Yes. That's correct.

03:35:49 10 Q And this is the indication that you were referring to a  
03:35:54 11 moment ago, right, about lipids?

03:35:56 12 A Yes, that was submitted with the original -- as part of  
03:36:00 13 the supplemental new drug application, yes.

03:36:03 14 Q Okay. And without repeating the entire indication, one  
03:36:08 15 portion of the indication that you were seeking approval for  
03:36:11 16 was the use of Vascepa as an adjunct to diet to reduce apo B  
03:36:19 17 right?

03:36:19 18 A In that stream.

03:36:21 19 Q Right.

03:36:21 20 A Yes, in that stream of parameters.

03:36:24 21 Q Okay. Then let's -- take a slight detour, DX 1558, pages  
03:36:32 22 4 and 5.

03:36:33 23 This is the complete response letter, right?

03:36:39 24 A That is the complete response letter.

03:36:42 25 Q Okay. So this letter went from FDA to you, right, on

03:36:46 1 April --

03:36:46 2 A Yes, on April 27th, 2015.

03:36:49 3 Q Exactly. Thank you. And that's why I have the date  
03:36:51 4 because the FDA puts the date all the way at the end instead  
03:36:56 5 of on the cover page for reasons I'll never understand.

03:36:59 6 But DDX 2.6 is -- we're going back -- this is the  
03:37:05 7 complete response letter DX 1558, right?

03:37:10 8 A This is DX 1558.

03:37:12 9 Q Right. And this is where the FDA determined that they  
03:37:16 10 cannot approved Amarin's application in its present form for  
03:37:20 11 the indication that included the use of Vascepa to reduce  
03:37:28 12 apo B, correct?

03:37:29 13 A Yes. This spells out FDA's reasons why they could not  
03:37:33 14 approve the SNDA.

03:37:35 15 Q Right. And let's go back to the dispute letter, which is  
03:37:43 16 DX 1836, let's go to page 70, it's a long document. This is  
03:37:49 17 DDX 2.61.

03:37:59 18 A Yes.

03:38:00 19 Q Okay. So given the strict regulatory requirements for  
03:38:03 20 FDA approval, FDA did not accept Amarin's reliance on the  
03:38:07 21 JELIS study to support the ANCHOR indication, right?

03:38:11 22 A Amarin did not rely on the JELIS results for its ANCHOR  
03:38:16 23 SNDA. The ANCHOR SNDA was based solely on the conditions of  
03:38:23 24 the SPA agreement which were ANCHOR focused on its safety and  
03:38:24 25 efficacy data, and on having a large, long-term outcomes trial

03:38:30 1 50 percent of the way in a multinational patient population.

03:38:35 2 Q I mean, Amarin certainly cited the JELIS study to the FDA  
03:38:40 3 in connection with this dispute, right?

03:38:41 4 A Amarin did mention JELIS, amongst other pieces in the  
03:38:47 5 scientific literature, in trying to appeal the SPA recission,  
03:38:53 6 that is correct.

03:38:54 7 Q And Amarin disagreed with FDA's views concerning the  
03:38:59 8 JELIS trial, right?

03:39:00 9 A They disagreed with certain of its views. Not all of its  
03:39:04 10 views.

03:39:05 11 Q Fair enough. Fair enough.

03:39:06 12 And so here we're in subsection D, DMEP, Assertion  
03:39:12 13 4,

03:39:12 14 "The JELIS trial results should be dismissed  
03:39:14 15 on the basis of design flaws and being inapplicable  
03:39:18 16 to United States population."

03:39:19 17 That's something that FDA said, right?

03:39:21 18 A Yes, amongst other things.

03:39:23 19 Q Right, and we'll get that.

03:39:25 20 And you say, "Counterpoints to these assertions are  
03:39:29 21 provided below," right?

03:39:31 22 A Yes, they are.

03:39:32 23 Q Let's go to DDX 2.62, this is page 70.

03:39:39 24 So the first counterpoint, counterpoint 4.1, is  
03:39:39 25 that,

03:39:43 1 "JELIS is the only trial with positive  
03:39:45 2 outcomes data for statin add-on therapy, and it used  
03:39:49 3 the same active ingredient for Vascepa," right?

03:39:52 4 A Yes, that's the phrasing of a counterpart to that FDA  
03:40:00 5 assertion that you previously had on the prior slide.

03:40:03 6 Q Right. And then you describe the JELIS study,  
03:40:08 7 "Compared to statin therapy alone (control),  
03:40:10 8 statin plus EPA treatment resulted in a significant  
03:40:14 9 19 percent relative risk reduction in the primary  
03:40:18 10 endpoint," right?

03:40:18 11 A Yes, in the context of -- this is an appendix on page 70  
03:40:24 12 of a document that -- so it's relegated to an appendix where  
03:40:28 13 we're trying to provide counterpoints to certain rather strong  
03:40:33 14 statements from FDA.

03:40:35 15 Q And even though was in the appendix, it's a truthful and  
03:40:38 16 accurate characterization of JELIS.

03:40:42 17 A Yes. Yes, it is, just that context I provided is  
03:40:45 18 important.

03:40:45 19 Q Okay. Let's go to the next slide which is DX 1837 [sic],  
03:40:50 20 page 71, which is DDX 2.63.

03:40:54 21 And here, you say,

03:40:55 22 "The JELIS investigators also performed a  
03:40:59 23 subanalysis of primary prevention patients with  
03:41:01 24 abnormal lipid levels," and then you defined them.

03:41:04 25 "Compared to patients with normal serum triglycerides



03:41:08 1 and HDL-C levels, those with abnormal levels had  
03:41:14 2 significantly higher coronary artery disease hazard  
03:41:18 3 ratio, and EPA treatment suppressed the risk of  
03:41:21 4 coronary artery disease by 53 percent in this higher  
03:41:25 5 risk population," right?

03:41:27 6 A Yes, I see those words.

03:41:28 7 Q Okay. That's a bit technical, but, in essence, Amarin  
03:41:31 8 was telling FDA that JELIS showed pure EPA achieved  
03:41:39 9 significant cardiovascular benefits, right?

03:41:39 10 A So I don't have that -- I have the cover letter to that  
03:41:43 11 exhibit in this binder. If I understand the overlays, this is  
03:41:47 12 from a different -- is this from the same --

03:41:51 13 Q This is from your dispute resolution request.

03:41:54 14 A Yes, but this isn't the prior --

03:41:57 15 THE COURT: I'm sorry, Mr. Klein, let me  
03:41:58 16 interrupt you for a moment. I thought you referenced this as  
03:42:01 17 coming from DX 1837, but I see that DX 1837 only has one page.  
03:42:07 18 Are you referring --

03:42:08 19 MR. KLEIN: Oh, this is a misnomer. I think  
03:42:10 20 it's 1836. I apologize. 1837 is the cover letter.

03:42:18 21 THE WITNESS: So this should be 1836, and it's  
03:42:23 22 page 71?

03:42:24 23 MR. KLEIN: This is page 71.

03:42:24 24 BY MR. KLEIN:

03:42:29 25 Q And I know this statement is technical, but let me try to

03:42:33 1 boil it down. You told FDA on behalf of Amarin that JELIS was  
03:42:38 2 a positive outcome study in which the primary endpoint was  
03:42:42 3 successful, correct?

03:42:43 4 A Yes. And, again, this is a counterpoint to an insertion  
03:42:48 5 that's entirely dismissive of JELIS saying it has absolutely  
03:42:51 6 no value and is totally inapplicable to the U.S. patient  
03:42:57 7 population. So this is a counterpoint to that assertion.

03:42:59 8 Q All right. And this Amarin's position to what FDA was  
03:43:02 9 saying, right?

03:43:02 10 A Yeah, in the face of that whole-scale dismissal.

03:43:05 11 Q Okay. And here it says,

03:43:09 12 "This 53 percent reduction represents a  
03:43:12 13 positive subgroup analysis derived from a positive  
03:43:17 14 outcome study in which the primary endpoint was  
03:43:17 15 successfully met."

03:43:19 16 That's what I -- I guess that's what I just  
03:43:20 17 asked you about, right? That's an accurate statement?

03:43:22 18 A It is, and particularly in contrast as stated in the  
03:43:27 19 prior sentences to what occurred in the niacin and fibrate  
03:43:31 20 studies which had a negative result on its primary endpoint  
03:43:35 21 and had positive indications from posthoc subgroup analyses.

03:43:41 22 So JELIS had some additional positive attributes  
03:43:47 23 relative to the other studies that they were trying to lump  
03:43:51 24 our product into the same bucket.

03:43:53 25 Q Let's go to DX 1836, page 72, DDX 2.65.

03:44:00 1 This is another counterpoint.

03:44:03 2 "JELIS was a very large, PROBE design study  
03:44:06 3 that included blinded endpoint evaluation," right?

03:44:10 4 A Yes, it did.

03:44:11 5 Q And PROBE stands for Prospective Randomized Open Label  
03:44:11 6 Blinded Endpoint Evaluation?

03:44:12 7 A Yes.

03:44:18 8 Q Sorry. I need to slow down.

03:44:24 9 Okay. And then you see the sentence starting  
03:44:27 10 "therefore"?

03:44:28 11 A Yes.

03:44:29 12 Q You told the FDA that,

03:44:31 13 "Therefore, overall, JELIS was a very large,  
03:44:34 14 well-designed study with blinded endpoint evaluation  
03:44:37 15 that demonstrated a statistically significant  
03:44:40 16 reduction in cardiovascular risk due to a statin  
03:44:45 17 add-on therapy," right?

03:44:46 18 A Yes. Amarin did say that as a counterpoint to an FDA  
03:44:49 19 assertion to the contrary.

03:44:51 20 Q This was actually a document that was submitted under  
03:44:54 21 your cover letter, right, so you actually said this, right?

03:44:57 22 A Yes. We sent it, again, and this is in the context of  
03:45:00 23 disputing the recission of the ANCHOR SPA where they were  
03:45:08 24 saying that because of failed trials of other agents in  
03:45:13 25 cardiovascular outcomes trials, that there were -- there was

03:45:16 1 scientific uncertainty that caused them to rescind our SPA.

03:45:22 2 Q Right.

03:45:22 3 A So we were pushing back on it.

03:45:24 4 Q And then -- so on page 71, DDX 2.66, you told the FDA  
03:45:35 5 that Amarin believes that its results, the JELIS results,  
03:45:41 6 should not be dismissed, lightly correct?

03:45:43 7 A Yes, that's correct.

03:45:44 8 Q In fact, that was Amarin's strongly held belief that FDA  
03:45:49 9 should not lightly dismiss the JELIS study results, correct?

03:45:52 10 A Again, in the context of them saying it had absolutely no  
03:45:56 11 value.

03:45:56 12 Q Okay. DDX 2.67, here's another counterpoint. We're on  
03:46:02 13 page 71 of DX 1836. And this counterpoint is,

03:46:05 14 "Precedent suggests that results from  
03:46:08 15 cardiovascular studies conducted in an exclusively  
03:46:11 16 Japanese population are applicable to the United  
03:46:14 17 States population," right?

03:46:15 18 That was a point that Amarin made to the FDA?

03:46:19 19 A Yes. And the counterpoints are structured because a part  
03:46:24 20 of FDA's assertion is that it's inapplicable to a US patient  
03:46:31 21 population.

03:46:31 22 Q Right. Understood. Each of these counterpoints are  
03:46:34 23 responding to a point that FDA made.

03:46:35 24 A To construct of their assertion.

03:46:37 25 Q Understood. If we go to page 72, DDX 2.68, this is

another counterpoint.

"Vascepa 4 grams per day in a United States-based population achieves similar plasma EPA levels as EPA 1.8 grams per day in a Japanese population," right?

A Yes. At the time this document was written, we had our MARINE results, our ANCHOR results.

We had subsequently, years later, published some plasma EPA level data. And years after the initial Yokoyama *Lancet* publication, they, in turn, published some level of information. So this is speaking to that -- to that -- those facts.

Q Okay. What you're saying is that a lower dose in a Japanese population can equate to a lower dose, specifically 1.8 grams per day, equates to the Vascepa dose 4 grams per day in the U.S., correct?

A Equates goes beyond the statement that's phrased there.

Q Comparable? Similar?

A Similar. And.

Q Similar. I'll take similar.

A And there are obviously differences --

Q Okay.

A -- between the dosage forms, et cetera.

Q DDX 2.69, this is page 73 of DX 1836, the next counterpoint is,

03:48:00 1 "LDL-C was adequately controlled for the  
03:48:00 2 majority of JELIS patients as it was treated  
03:48:00 3 according to JAS guidelines."

03:48:00 4 That's the Japanese Atherosclerosis Society  
03:48:13 5 guidelines, right?

03:48:13 6 A Yes, that's correct.

03:48:15 7 Q Okay. And, generally speaking, you told FDA that JELIS  
03:48:27 8 was a very large, well-designed study demonstrating that  
03:48:31 9 Vascepa would support -- helping convince the FDA that Vascepa  
03:48:36 10 would significantly reduce cardiovascular events, right?

03:48:39 11 A Again, in the backdrop of having an approved MARINE  
03:48:42 12 indication, so a successful MARINE trial, a successful ANCHOR  
03:48:48 13 trial for which we had submitted supplemental new drug  
03:48:52 14 application totally consistent with our special protocol  
03:48:57 15 assessment agreement with FDA, so those were the core points  
03:48:59 16 that we raised earlier on within the document.

03:49:02 17 These are relegated to an appendix because they are  
03:49:06 18 additional arguments that we're putting fourth to  
03:49:10 19 counterassert certain rather strong and definitive statements  
03:49:15 20 from FDA.

03:49:15 21 THE COURT: Dr. Ketchum, I want to make sure you  
03:49:18 22 listen to the question and limit your answer to the question,  
03:49:21 23 otherwise you'll be here extensively tomorrow as well.

03:49:24 24 THE WITNESS: Yes, Your Honor. I understand.

25 ///

03:49:27 1 BY MR. KLEIN:

03:49:27 2 Q Let's look at the conclusion, okay? To move this on.  
03:49:30 3 DX 1836, page 80, is the DDX 2.70.

03:49:36 4 The conclusions actually run several paragraphs. So  
03:49:40 5 if we go the next slide, this is the fourth point in the  
03:49:43 6 conclusion, page 81, DDX 2.71.

03:49:46 7 You see here Amarin is telling the FDA,  
03:49:49 8 "JELIS is the single cardiovascular outcome  
03:49:54 9 study that has demonstrated a cardiovascular benefit  
03:49:54 10 of a statin add-on therapy. Despite some design  
03:50:01 11 constraints, JELIS is very large, well-designed study  
03:50:04 12 that demonstrated a significant improvement in its  
03:50:08 13 primary endpoint and in subsequent subgroup analyses,  
03:50:08 14 such as a 53 percent reduction in cardiovascular  
03:50:15 15 events in patients with elevated baseline  
03:50:18 16 triglyceride and low baseline HDL-C."

03:50:23 17 That was accurate statement to the FDA, correct?

03:50:26 18 A Yes.

03:50:26 19 Q At the end of this paragraph you tell the FDA that,  
03:50:29 20 "These points strongly support the  
03:50:32 21 consideration of JELIS study results in evaluating  
03:50:36 22 the potential cardiovascular benefits of Vascepa  
03:50:42 23 therapy," right?

03:50:43 24 A Yes, that's the statement.

03:50:43 25 Q And Amarin was making all these statements with regard to

03:50:46 1 JELIS, painting JELIS in a positive light, to try to convince  
03:50:51 2 FDA to take favorable regulatory action, correct?

03:50:55 3 A It was amongst those arguments, yes.

03:50:59 4 Q I want to go to one of the documents that we looked at,  
03:51:04 5 or you looked at during the direct examination.

03:51:07 6 MR. KLEIN: Mr. Gross, can you put up PX 990,  
03:51:12 7 please.

03:51:12 8 BY MR. KLEIN:

03:51:18 9 Q Just to orient you, do you remember this document to you  
03:51:21 10 from FDA, the appeal denied letter?

03:51:24 11 A Yes.

03:51:26 12 MR. KLEIN: Okay. And if we go to PX 990,  
03:51:30 13 page 11 -- and can you highlight that? Yeah.

03:51:30 14 BY MR. KLEIN:

03:51:35 15 Q Do you remember talking about this paragraph?

03:51:40 16 A Yes.

03:51:41 17 Q Okay. And you were talking about how FDA was criticizing  
03:51:47 18 the JELIS study, right?

03:51:49 19 A Yes.

03:51:50 20 Q But there are some statements in this paragraph where the  
03:51:53 21 FDA talked about how there were positive results on clinical  
03:51:58 22 benefit from JELIS, right? That's what the FDA found?

03:52:03 23 A That's what that statement is referring to, yes.

03:52:05 24 Q Right. And then this statement below says,

03:52:07 25 "This trial may be supportive in reducing



03:52:11 1 cardiovascular events with the use of EPA for those  
03:52:14 2 patients taking baseline low intensity statins,"  
03:52:19 3 right?

03:52:19 4 A That's what that sentence says.

03:52:20 5 Q But FDA did not believe that JELIS was run according to  
03:52:25 6 the very high bar of FDA standards for clinical trials,  
03:52:30 7 correct?

03:52:30 8 A That's correct.

03:52:34 9 MR. KLEIN: Let's go back to the slide deck.

03:52:47 10 Okay. Let's go to DX 1838, and this is  
03:52:54 11 demonstrative DDX 2.73.

03:52:54 12 BY MR. KLEIN:

03:52:58 13 Q Do you recognize this as a PowerPoint presentation  
03:53:02 14 presented at a 2017 national meeting?

03:53:05 15 A Yes, I do.

03:53:06 16 Q And you presented this with Dr. Rebecca Juliano?

03:53:11 17 A Yes.

03:53:12 18 Q And the presentation is on REDUCE-IT, right?

03:53:16 19 A It is.

03:53:16 20 Q Is this an Amarin national meeting?

03:53:18 21 A This is a sales national meeting of Amarin employees.

03:53:28 22 Q I see. It's an internal Amarin meeting?

03:53:30 23 A Yes, it's an internal Amarin meeting.

03:53:32 24 Q Okay. And you're obviously the Steve Ketchum on the  
03:53:35 25 slide deck, right?

03:53:36 1 A I am, yes.

03:53:37 2 Q If we go to DX 1838, page 8, which is DDX 2.74, there's a  
03:53:45 3 slide called EPA Benefit in CHD Risk Supported By JELIS Trial.  
03:53:51 4 Do you see that?

03:53:51 5 A Yes.

03:53:53 6 Q And CHD stands for coronary heart disease, right?

03:53:57 7 A That's correct.

03:53:57 8 Q And this slide summarizes the JELIS trial, right?

03:53:57 9 A From -- the source publication is highlighted in the  
03:54:01 10 bottom.

03:54:02 11 Q Right. And the chart on the left says the cumulative  
03:54:06 12 incidence of major coronary events decreased by 19 percent in  
03:54:10 13 the JELIS trial, right?

03:54:12 14 A Yes.

03:54:12 15 Q And that's citing Yokoyama, *The Lancet* article?

03:54:16 16 A Yes.

03:54:17 17 Q And the subgroup on the right says that the cumulative  
03:54:20 18 incidents of major coronary events was reduced by 53 percent  
03:54:25 19 according to the subgroup analysis, right?

03:54:27 20 A Yes.

03:54:28 21 Q And that's citing a reference called Saito dated 2008,  
03:54:33 22 right?

03:54:33 23 A That's correct.

03:54:37 24 Q If we go DDX 2.75, this is DX 1838, page 9, the title of  
03:54:44 25 this slide is REDUCE-IT Design is Well Informed, right?

03:54:48 1 A Yes.

03:54:49 2 Q And it says -- the second bullet says,

03:54:52 3 "Events driven study design incorporates  
03:54:56 4 learnings from the positive JELIS study (Japan  
03:55:01 5 cardiovascular outcomes study of EPA) and other well  
03:55:05 6 designed CVOTs," right?

03:55:07 7 A Yes.

03:55:07 8 Q What is CVOTs?

03:55:10 9 A Cardiovascular outcomes trials.

03:55:12 10 Q Okay. And then the sub bullet says, "JELIS administered  
03:55:14 11 ethyl-EPA; same active component as Vascepa."

03:55:19 12 You see that, right?

03:55:19 13 A Yes, I see that.

03:55:21 14 Q Okay. And so you told everyone who attended this 2017  
03:55:24 15 annual meeting that JELIS was a positive study, correct?

03:55:27 16 A Yes.

03:55:29 17 Q And you also told them that JELIS administered ethyl-EPA  
03:55:34 18 which is the same active component at Vascepa, correct?

03:55:38 19 A Yes.

03:55:44 20 Q Let's go to DX 2252, and the slide is 2.76.

03:55:50 21 Do you recognize this as a section of Amarin's  
03:55:54 22 March 29 supplemental NDA submission?

03:56:00 23 A Yes.

03:56:00 24 Q Let's go to DX 2252, page 9, which is DDX 2.77, and we're  
03:56:09 25 looking at section 2.7.3, Summary of Clinical Efficacy, right?

03:56:16 1 A Yes.

03:56:16 2 Q And if we go further into this section, DX 2252, page 62,  
03:56:22 3 which is DDX 2.78, there's a statement that,

03:56:27 4 "Administration of ethyl-EPA plus statins in  
03:56:31 5 JELIS resulted in 19 percent relative reduction in  
03:56:34 6 the risk of major coronary events despite a  
03:56:38 7 relatively small (5 percent) reduction in TG  
03:56:42 8 (Yokoyama 2007), suggesting the effects of EPA  
03:56:47 9 therapy on cardiovascular outcomes likely go beyond  
03:56:52 10 traditional clinical lipid modification," right?

03:56:55 11 A Yes. The five percent results didn't seem to explain the  
03:56:59 12 19 percent.

03:56:59 13 Q Okay. But this is what you told the --

03:57:02 14 A That's correct.

03:57:01 15 Q -- FDA, correct?

03:57:03 16 A Yeah, that's what it's conveying.

03:57:05 17 Q Right, in the context of seeking approval of your  
03:57:08 18 supplement NDA, correct?

03:57:10 19 A Yes.

03:57:10 20 Q And if we go to DDX 2.79, which is page 62, you say,

03:57:17 21 "In agreement, initial REDUCE-IT subgroup  
03:57:20 22 analyses of TG levels at study baseline and achieved  
03:57:25 23 at one year suggest that the effects of EPA therapy  
03:57:28 24 on CV outcomes likely go beyond TG lowering and are  
03:57:34 25 distinct from other therapies that lower TG levels,"

03:57:40 1 right?

03:57:40 2 A Yes.

03:57:41 3 Q And so what you're saying is -- to the FDA is that the  
03:57:45 4 explanation for the cardiovascular benefits observed in JELIS  
03:57:50 5 is in agreement with the explanation for the cardiovascular  
03:57:54 6 benefit observed in REDUCE-IT, correct?

03:57:57 7 A What we're saying there are some similarities, yes.

03:58:00 8 Q Let's go to page 63 of DX 2252, DDX 2.80.

03:58:07 9 Here, Amarin is telling the FDA that,

03:58:12 10 "JELIS evaluated statin alone (no placebo) in  
03:58:17 11 the control arm, but the ethyl-EPA preparation  
03:58:20 12 demonstrated substantial coronary risk reduction  
03:58:23 13 similar to Vascepa in REDUCE-IT," correct?

03:58:26 14 A Yes.

03:58:29 15 Q And so Amarin told FDA that the coronary risk reduction  
03:58:34 16 observed in JELIS is similar to that in observed with Vascepa  
03:58:40 17 in REDUCE-IT, right?

03:58:41 18 A It's -- the purpose of that section is to say that the  
03:58:45 19 use of the placebo in REDUCE-IT is not the explanation for why  
03:58:51 20 we observed a 25 percent relative risk reduction.

03:58:56 21 Q Right. Okay. Let's go to a new document, DX 2226, which  
03:59:02 22 is demonstrative DDX 2.81.

03:59:08 23 And do you recognize this as the Endocrinologic and  
03:59:15 24 Metabolic Drugs Advisory Committee Briefing Document, dated  
03:59:19 25 November 14th, 2019?

03:59:21 1 A Yes, I do.

03:59:21 2 Q Okay. This was the briefing document for the advisory  
03:59:24 3 committee related to Amarin's supplemental NDA, right?

03:59:29 4 A That's correct.

03:59:30 5 Q Okay. And let's go to DX 2226, page 6, slide DDX 2.82.

03:59:36 6 And here Amarin is -- or -- yeah, this is created by  
03:59:43 7 Amarin, right, this briefing document?

03:59:46 8 A I'm sorry, could I see the cover page again?

03:59:50 9 Q Sure.

03:59:51 10 A This -- yes, this is Amarin's briefing document.

03:59:58 11 Q Okay. And Amarin is saying that.

03:59:59 12 "...a 25 percent RRR," relative risk  
04:00:03 13 reduction, "in the primary endpoint that is  
04:00:05 14 consistent with the observed risk reduction in the  
04:00:09 15 Japan EPA JELIS study," right?

04:00:13 16 A Yes.

04:00:13 17 Q And Amarin made this comparison of REDUCE-IT to JELIS to  
04:00:18 18 support favorable regulatory action, in particular, approval  
04:00:22 19 of the supplemental NDA, correct?

04:00:24 20 A Principally to put the placebo aspect into context.

04:00:29 21 Q Now, let's go to another document, DX 2235, and it's  
04:00:34 22 slide DDX 2.83.

04:00:36 23 Do you recognize this as a presentation to the FDA  
04:00:39 24 advisory committee that was considering Amarin's supplemental  
04:00:44 25 NDA?

04:00:44 1 A Yes, I do.

04:00:45 2 Q All right. Let's turn to DX 2235, page 70, which is  
04:00:51 3 DDX 2.84, and this is a slide called Mineral Oil Placebo  
04:00:55 4 Analyses, right?

04:00:57 5 A Yes.

04:00:57 6 Q And the last bullet says,

04:01:00 7 "Prior trial reported a cardiovascular  
04:01:02 8 benefit with EPA consistent with REDUCE-IT," right?

04:01:05 9 A Yes.

04:01:06 10 Q And the prior trial that's consistent with REDUCE-IT  
04:01:10 11 that's being referenced is the JELIS study, right?

04:01:13 12 A That's correct.

04:01:23 13 Q All right. Let's go -- well, let's back up.

04:01:27 14 In December 2019, FDA approved the supplemental NDA,  
04:01:31 15 right?

04:01:31 16 A Yes.

04:01:32 17 Q And that resulted in what you call the REDUCE-IT  
04:01:34 18 indication, right?

04:01:35 19 A Yes.

04:01:35 20 Q And then FDA approved the new Vascepa label?

04:01:40 21 A Yes.

04:01:41 22 Q But FDA did not approve the precise indication that  
04:01:45 23 Amarin had proposed, right?

04:01:47 24 A That's very common, but, yes.

04:01:49 25 Q I'm not saying whether it's common or not.

04:01:52 1 A Uh-huh.

04:01:53 2 Q But let's turn -- just so we can determine what the  
04:01:57 3 distinctions are, on the left is DX 2247. That's the proposed  
04:02:04 4 label that Amarin submitted in March 2019, right?

04:02:08 5 A Yes.

04:02:09 6 Q Okay. So that's the proposed REDUCE-IT indication,  
04:02:13 7 right?

04:02:14 8 A In the SNDA, yes.

04:02:17 9 Q Right. And on the right DX 2248, and, by the way, this  
04:02:21 10 is DDX 2.85, on the right is what is now the REDUCE-IT  
04:02:26 11 indication, correct?

04:02:28 12 A Yes.

04:02:28 13 Q Okay. And so Amarin sought approval for Vascepa to,  
04:02:32 14 among other things, reduce the risk of cardiovascular death  
04:02:37 15 right?

04:02:37 16 A Yes, that was one of the endpoints study.

04:02:40 17 Q Okay. And FDA did not approve that indication, right?

04:02:43 18 A Not in the stream of -- that's listed within the  
04:02:49 19 indication.

04:02:49 20 Q Right. And Amarin sought approval for Vascepa in adult  
04:02:55 21 patients with elevated triglyceride levels greater or equal to  
04:02:57 22 135 milligrams per deciliter and other risk factors for  
04:03:02 23 cardiovascular disease, right?

04:03:05 24 A Yes, that's what we proposed.

04:03:08 25 Q And FDA determined that the approved patient population



04:03:11 1 should be limited to patients with triglyceride levels above  
04:03:14 2 150 with either established cardiovascular disease or diabetes  
04:03:20 3 plus two or more additional risk factors for cardiovascular  
04:03:25 4 disease; is that right?

04:03:26 5 A At the indication level.

04:03:28 6 Q Yes, right.

04:03:29 7 A As opposed to other sections.

04:03:31 8 Q Okay. Now, I want to talk about something that was  
04:03:34 9 covered on direct, but I just want to clarify a couple of  
04:03:37 10 points.

04:03:38 11 On direct you talked about how in March 2019, Amarin  
04:03:41 12 had proposed a section 6.2 postmarketing experience, right?

04:03:47 13 A Yes.

04:03:47 14 Q And that's DX 2247, and then in the final label, the FDA  
04:03:55 15 made some change, right?

04:03:57 16 A Yes.

04:03:57 17 Q And that is DX 2248, and, for the record, this is  
04:04:04 18 DDX 2.86.

04:04:05 19 And the highlighted section that Amarin proposed  
04:04:08 20 was,

04:04:09 21 "Because these reactions are reported  
04:04:11 22 voluntarily from a chronic care population of  
04:04:15 23 uncertain size."

04:04:17 24 Do you see that?

04:04:17 25 A Yes I see that.

04:04:18 1 Q And the only thing that the FDA struck was the term  
04:04:22 2 chronic care.

04:04:23 3 A Yes.

04:04:24 4 Q And you don't know why FDA struck it because they didn't  
04:04:27 5 tell you, right?

04:04:28 6 A That's correct.

04:04:28 7 Q Right. But, as a result, the Vascepa label does not  
04:04:35 8 refer to the patient population as requiring chronic care,  
04:04:40 9 right?

04:04:40 10 A Those words are not in that specific section of the  
04:04:44 11 label.

04:04:45 12 Q And the Vascepa label, the current Vascepa label, does  
04:04:48 13 not ever say that patients were severe hypertriglyceridemia  
04:04:53 14 have a chronic condition, correct?

04:04:55 15 A It's supported by the statements we walked through  
04:05:00 16 earlier this morning in terms of the checklist and the  
04:05:03 17 development requirements.

04:05:05 18 Q Please listen to the question carefully.

04:05:07 19 The Vascepa label as approved does not say that  
04:05:12 20 severe hypertriglyceridemia is a chronic condition, correct?

04:05:16 21 A It does not use those words.

04:05:22 22 Q And let's go back to a document that you covered on  
04:05:26 23 direct, PX 286.

04:05:47 24 Do you remember this document, the -- I forget what  
04:05:52 25 you call it, the sound board? Is that what --

04:05:54 1 A Storyboard.

04:05:55 2 Q Storyboard. Thank you. Storyboard for the commercial.

04:05:55 3 A Yes.

04:06:00 4 Q And you talked about how in the commercial it mentions  
04:06:03 5 no -- without raising LDL-C versus placebo, do you remember  
04:06:09 6 that?

04:06:09 7 A Yes, I believe it was frame 11.

04:06:12 8 Q It's a simple question.

04:06:15 9 A Yes.

04:06:15 10 Q Amarin's commercials don't advertise that Vascepa lowers  
04:06:23 11 apo B, correct?

04:06:24 12 A These specific advertisements is what your asking me  
04:06:27 13 about?

04:06:27 14 Q Yes.

04:06:28 15 A These specific advertisements do not.

04:06:31 16 Q All right. Let's go back to the slide deck. Let's go to  
04:06:44 17 DX 2267, and, for the record, it's demonstrative DDX 2.87.

04:06:55 18 Before I ask you to explain what this document is,  
04:06:58 19 you understand that when FDA approves a new indication the  
04:07:02 20 sponsor of the application needs to notify the FDA of any  
04:07:06 21 relevant patents.

04:07:07 22 A Yes.

04:07:07 23 Q It's generally referred to as patent information, right?

04:07:12 24 A Yes.

04:07:14 25 Q Okay. And then what FDA does is FDA takes the

04:07:19 1 information from the NDA holder, the patent information, and  
04:07:23 2 publishes it in what's referred to as the Orange Book, right?

04:07:27 3 A Yes.

04:07:28 4 Q Okay. But the Orange Book is actually online?

04:07:30 5 A It is online.

04:07:31 6 Q Okay. And you recognize DX 2267 as the Orange Book  
04:07:40 7 patent listing for Vascepa, right?

04:07:43 8 A As of some specific date that I'm not familiar with.  
04:07:50 9 But, yes, I recognize that as the patent listing.

04:07:52 10 THE COURT: Mr. Klein, I have a question for  
04:07:54 11 you.

04:07:54 12 MR. KLEIN: Sure.

04:07:54 13 THE COURT: The exhibits that were offered to  
04:07:56 14 the Court by the parties, both in the exhibit list and the  
04:08:00 15 actual exhibits for defendants, end at DX 2265.

04:08:05 16 MR. KLEIN: Yes, this was a new exhibit. I  
04:08:08 17 think -- did we provide a thumb drive to someone? This is a  
04:08:12 18 new exhibit because it was recently created.

04:08:15 19 THE CLERK: Your Honor, they did provide a thumb  
04:08:18 20 drive, they have not provided an updated exhibit list to my  
04:08:22 21 knowledge.

04:08:23 22 MR. KLEIN: Okay. We can do that.

04:08:24 23 THE COURT: That's all right. I want to make  
04:08:26 24 sure that I receive any exhibits. So a thumb drive was  
04:08:30 25 provided with the additional exhibits?

04:08:33 1 MR. KLEIN: Yes, Your Honor.

04:08:33 2 THE CLERK: Yes. Two copies.

04:08:33 3 BY MR. KLEIN:

04:08:34 4 Q And I can clarify. The Orange Book listing for Vascepa  
04:08:39 5 was updated very recently, right?

04:08:41 6 A Yes.

04:08:41 7 Q And that's because the new indication was approved in  
04:08:45 8 December.

04:08:45 9 A That's correct.

04:08:45 10 Q And -- but you recognize this as the current Orange Book  
04:08:49 11 listing? Does it look right? I'll represent to you that we  
04:08:52 12 did our best to print out the most recent one.

04:08:55 13 A Yes. So my regulatory affairs team takes the information  
04:09:00 14 from intellectual property lawyers and helps to progress the  
04:09:03 15 submission. So this appears to be the Orange Book listing  
04:09:10 16 that incorporates the latest information submitted on  
04:09:13 17 January 6th.

04:09:14 18 Q Okay. And by my count, Amarin has listed 46 patents as  
04:09:17 19 related to Vascepa, does that sound about right?

04:09:20 20 A Yeah. I haven't counted, but I'll take your word for  
04:09:23 21 that.

04:09:24 22 Q Okay. And you understand that there are forms that  
04:09:26 23 Amarin has to submit to the FDA that links the patent to  
04:09:32 24 particular indications or methods of use, right?

04:09:35 25 A Yes, I understand that.

04:09:37 1 Q Okay. So, generally speaking, these patents are  
04:09:40 2 associated either with the MARINE indication or the REDUCE-IT  
04:09:44 3 indication, right?

04:09:46 4 A Or some other category of patent. Again, I'm not the  
04:09:51 5 inventor on any of these patents so I'm not as familiar with  
04:09:55 6 the details.

04:09:56 7 Q Are you ultimately responsible for their submissions to  
04:10:01 8 the FDA on this point?

04:10:02 9 A Yes, but there are other parties who are more familiar  
04:10:07 10 from an intellectual property perspective who help us to  
04:10:07 11 confirm that the details are accurate prior to submission.

04:10:11 12 Q But you generally understand that in the patent  
04:10:14 13 information submitted to the FDA, Amarin tied patents either  
04:10:18 14 to the MARINE indication or to the REDUCE-IT indication,  
04:10:21 15 right?

04:10:21 16 A Generally speaking, yes.

04:10:25 17 MR. KLEIN: Okay. And let's go to -- we've  
04:10:30 18 marked this as DX 2299, and I will move to admit it as a  
04:10:34 19 summary exhibit. There may be objection, and, if so, we'll  
04:10:39 20 deal with it at the end, but at a minimum it's a demonstrative  
04:10:44 21 exhibit, DDX 2.88.

04:10:44 22 BY MR. KLEIN:

04:10:46 23 Q Do you have DX 2299 in your binder?

04:10:49 24 A I do, yes.

04:10:49 25 Q Okay. Do you recognize that as the patent information

04:10:53 1 that's submitted to the FDA?

04:10:54 2 A Again, in looking at an Orange Book listing, I haven't  
04:11:00 3 sorted them out and done this diagram myself.

04:11:05 4 Q No, no, I asked you if you recognize DX 2250 as the  
04:11:09 5 patent information that Amarin submitted to the FDA.

04:11:13 6 A 2250.

04:11:14 7 Q 2250. Oh, oh, it's actually not in your binder.

04:11:26 8 It's voluminous because it's a number -- it relates  
04:11:29 9 to a number of patents, right, that were just recently listed?

04:11:33 10 A Yes, a number of patents were just recently listed.

04:11:37 11 Q Okay. And do you generally understand that none of the  
04:11:40 12 patents that are asserted in this case have been associated  
04:11:44 13 with the REDUCE-IT indication?

04:11:48 14 A So my -- again, in my role as the head of R&D, I'm not an  
04:11:56 15 intellectual property expert so I'm not defining  
04:12:01 16 overlappingness or, you know, being involved in these various  
04:12:06 17 assertions.

04:12:07 18 Q Okay.

04:12:07 19 A I'm not an expert in that area.

04:12:09 20 Q And so you have no knowledge as to whether, from a  
04:12:13 21 regulatory standpoint, the patents that -- that are asserted  
04:12:18 22 in this case are associated with the REDUCE-IT indication from  
04:12:25 23 a regulatory perspective.

04:12:27 24 A So from a regulatory perspective, my staff and I have  
04:12:31 25 been involved to the extent to confirm that the list is

04:12:34 1 accurate, meets intellectual property considerations and have  
04:12:39 2 been filed consistent with FDA requirements. That's the level  
04:12:43 3 of my involvement in that patent related process.

04:12:47 4 Q Okay. But do you generally understand that Amarin has a  
04:12:50 5 number of patents that are covering the REDUCE-IT indication?

04:12:54 6 A Yes, I do.

04:12:55 7 Q And those patents are not also covering the MARINE  
04:13:00 8 indication, correct?

04:13:00 9 A I am not aware of the details of the various patent  
04:13:05 10 families so I don't -- I don't know what to what extent they  
04:13:10 11 might overlap.

04:13:11 12 Q Okay. To your knowledge -- well, that's fine.

04:13:20 13 MR. KLEIN: All right. Let's -- I want to mark  
04:13:23 14 a slide. This is not in evidence, and I'm marking it just for  
04:13:30 15 identification, it's DX 2297. I'm using it as demonstrative,  
04:13:38 16 and it's DDX 2.89.

04:13:38 17 BY MR. KLEIN:

04:13:41 18 Q Do you generally recognize this Investor Relations Amarin  
04:13:44 19 document?

04:13:45 20 A Yes, I do.

04:13:45 21 Q And you see it's dated February 16th, 2012?

04:13:49 22 A Yes.

04:13:49 23 Q Okay. Let's go to the next slide, which is DDX 2.9, and  
04:13:56 24 that's when you were hired by Amarin, right?

04:13:58 25 A Yes, that was in the time frame when I was hired.



04:14:03 1 Q And when you were hired you received a grant of Amarin  
04:14:13 2 stock, correct?

04:14:13 3 A Of options.

04:14:15 4 Q Options, I'm sorry, you're right.

04:14:17 5 And it says,

04:14:17 6 "The grant to Dr. Ketchum consisted of  
04:14:20 7 nonqualified options to purchase 600,000 shares of  
04:14:24 8 the Amarin ordinary shares represented by the  
04:14:27 9 American Depository shares with a ten-year term and  
04:14:32 10 then an exercise price equal to the closing price of  
04:14:36 11 Amarin American Depository receipts on the date of  
04:14:40 12 grant," right?

04:14:41 13 A Yes.

04:14:42 14 Q And so, in essence, you were given options to purchase  
04:14:49 15 600,000 shares with is a ten-year term, correct?

04:14:51 16 A Yes.

04:14:51 17 Q And all these 600,000 shares will vest in February '22?

04:14:59 18 A I'd have to look at the way this subsequent -- it spells  
04:15:02 19 out what tranches would become available across what time  
04:15:06 20 frame.

04:15:06 21 Q I'm just going off it's ten years.

04:15:08 22 A Ten years.

04:15:09 23 Q And it's February 2012.

04:15:11 24 A I think that's speaking to the ten-year term of the  
04:15:14 25 options.

04:15:14 1 Q I see. Okay.

04:15:15 2 A The vesting is spelled out in the subsequent sentences.

04:15:19 3 Q All right.

04:15:20 4 A About the period of time.

04:15:22 5 Q I'll go to another slide, DX 2298 for identification, and  
04:15:27 6 it's DDX 2.91. I will represent to you that I took this from  
04:15:34 7 Yahoo! Finance. Okay. I'll ask you if it's correct.

04:15:46 8 According to this document, you currently have  
04:15:54 9 400 -- about 454,000 shares of Amarin stock; is that right?

04:15:59 10 A I don't know the precise number, but it is publically  
04:16:03 11 available information.

04:16:05 12 Q Okay. And you own more Amarin stock than any other  
04:16:10 13 employee except for the CEO, correct?

04:16:12 14 A Again, I don't know that for sure, but it's publically  
04:16:16 15 available information.

04:16:18 16 Q You have no reason to doubt -- the information on the  
04:16:21 17 screen looks generally correct to you, right?

04:16:23 18 A It looks -- assuming it's pulled from publicly available  
04:16:29 19 sources, it looks generally correct.

04:16:32 20 Q Okay. And I haven't checked the stock price today, but  
04:16:36 21 over the weekend it was about \$19 a share. Does that sound  
04:16:40 22 about right?

04:16:41 23 A Sounds about right.

04:16:42 24 Q And if my math is correct, your Amarin stock is currently  
04:16:46 25 valued at about eight and-a-half million dollars; is that

04:16:49 1 right?

04:16:49 2 A I haven't done the math, but if you have, that might be  
04:16:53 3 the approximate value at this point in time.

04:16:56 4 Q Do you have a general understanding about the value of  
04:16:59 5 your Amarin stock?

04:17:00 6 A It's not -- I'm focused on taking care of my R&D  
04:17:04 7 responsibilities. I've learned through my years in the  
04:17:06 8 industry that this is a standard mix of compensation, and I  
04:17:11 9 don't focus on it too much.

04:17:13 10 Q Okay. But it's somewhere in the neighborhood of 8 to  
04:17:17 11 \$10 million, correct?

04:17:18 12 A Subject to whatever taxes, et cetera. So there are other  
04:17:22 13 considerations that would diminish that number.

04:17:26 14 Q And you understand that the outcome of this litigation  
04:17:30 15 could dramatically affect the stock price, right?

04:17:34 16 A Over the eight years of my employment with Amarin there  
04:17:37 17 have been many milestones or occurrences that could impact the  
04:17:42 18 stock, so, again, I'm not focused on that.

04:17:45 19 Q Okay. But it's safe to say, sir, that you have a very  
04:17:48 20 large financial interest in the outcome of this litigation?

04:17:53 21 A I have a financial stake in Amarin.

04:17:58 22 Q And --

04:17:59 23 A Yes, I do.

04:17:59 24 Q And that financial stake can turn on this litigation,  
04:18:04 25 correct?

04:18:04 1 A Turn? I don't know what is meant by the --

04:18:07 2 Q Sir, do you have a general understanding that if you lose  
04:18:11 3 this case, and the generics get on the market within the next  
04:18:15 4 couple of months, that Amarin's stock may decrease  
04:18:17 5 significantly?

04:18:18 6 A I have an understanding that there are things that can  
04:18:22 7 impact Amarin's business, and I'm focused on playing my role  
04:18:25 8 in that business.

04:18:26 9 Q Fair enough, but you certainly have a financial interest  
04:18:29 10 in the case, correct?

04:18:30 11 A By virtue of owning stock in Amarin, yes, I have a  
04:18:34 12 financial interest in this case and any other business that  
04:18:37 13 Amarin conducts.

04:18:38 14 MR. KLEIN: Okay. No further questions, Your  
04:18:38 15 Honor.

04:18:44 16 THE COURT: Are you moving to admit any of the  
04:18:46 17 exhibits you referenced?

04:18:47 18 MR. KLEIN: Yes. Thank you. Thank you, Your  
04:18:50 19 Honor.

04:18:50 20 Yes, we move DX 1809, 1558 -- these are all DX  
04:18:55 21 numbers.

04:18:55 22 THE COURT: I'm sorry, so this is why I was  
04:18:57 23 concerned earlier when you said you wanted to -- because now I  
04:19:00 24 have to make sure that whatever exhibits you're referencing  
04:19:03 25 you did reference.

04:19:05 1 Are you about to read a list of exhibits that  
04:19:07 2 you referenced?

04:19:08 3 MR. KLEIN: Yes. These are the exhibits I  
04:19:10 4 referenced in the testimony.

04:19:11 5 THE COURT: Give me one -- I'll let you read it,  
04:19:14 6 but I think I need to verify my notes unless there's no  
04:19:18 7 objection before I rule. But why don't you read your exhibits  
04:19:22 8 slowly so Miss Clerk can take notes as to what exhibits have  
04:19:26 9 been identified.

04:19:27 10 MR. KLEIN: Okay. DX 1809 -- and, again, these  
04:19:28 11 are all DX 1809 numbers, 1558, 1800, 1809, 1814, 1816, 1829,  
04:19:42 12 1836, 1837, 1838, 2104, 2226, 2235, 2241, 2247, 2248, 2250,  
04:20:04 13 2252, 2255, 2267, and 2299.

04:20:12 14 And we also --

04:20:15 15 THE COURT: 2299 was a demonstrative that you  
04:20:18 16 didn't even ask any question on? Is this the one where you  
04:20:21 17 had the two charts. Are you seeking to admit that  
04:20:23 18 demonstrative exhibit?

04:20:25 19 MR. KLEIN: Yes, I did ask questions about  
04:20:27 20 that --

04:20:27 21 THE COURT: Well, you started to ask questions,  
04:20:29 22 then you referred to the copies of the patents that are  
04:20:32 23 attached as Exhibit DX 2250, and I don't recall you going back  
04:20:36 24 to 2299.

04:20:39 25 MR. KLEIN: That summary exhibit was a summary

04:20:41 1 exhibit of that document.

04:20:42 2 THE COURT: All right. So keep reading I'll see  
04:20:44 3 if there's any objection. So 2299?

04:20:47 4 MR. KLEIN: And 2250.

04:20:53 5 THE COURT: All right. Ms. Keane, do you have  
04:20:56 6 any objection?

04:20:58 7 MS. KEANE: Yes, Your Honor.

04:20:58 8 So, first of all, DX 2250, I don't think we saw  
04:21:04 9 that during the examination.

04:21:06 10 THE COURT: I'm sorry, which one?

04:21:09 11 MS. KEANE: DX 2250.

04:21:11 12 THE COURT: What is your -- you said you  
04:21:13 13 would -- didn't see that exhibit referenced?

04:21:16 14 MS. KEANE: Not during this examination, no.

04:21:26 15 THE COURT: I thought 2250 was a patent.

04:21:29 16 MR. KLEIN: I think 2250 is this --

04:21:33 17 THE COURT: It was referenced right around the  
04:21:37 18 time --

04:21:37 19 MR. KLEIN: This summary --

04:21:38 20 THE COURT: Hang on, let's not talk over each  
04:21:40 21 other. It's the end of the day, I don't want to make it too  
04:21:44 22 difficult for our court reporter.

04:21:45 23 2250 was referenced around the same time that  
04:21:48 24 2299 was offered.

04:21:50 25 MR. KLEIN: Correct, they're related.

04:21:51 1 THE COURT: That's a copy of all the patents.

04:21:54 2 MR. KLEIN: 2250 is the patent information that  
04:21:58 3 forms the basis for the summary exhibit which is 2299.

04:22:02 4 THE COURT: So, Ms. Keane, what's your objection  
04:22:04 5 to 2250?

04:22:05 6 MS. KEANE: So, yes, Your Honor, DX 2250 was not  
04:22:09 7 in the witness binder so it's not shown to the witness, and  
04:22:12 8 there's no foundation with this witness to admit that into  
04:22:15 9 evidence.

04:22:15 10 MR. KLEIN: I do think a foundation was  
04:22:18 11 established that the witness is actually in charge, ultimately  
04:22:21 12 in charge of filing these forms.

04:22:23 13 MS. KEANE: And then he pointed out that he does  
04:22:25 14 not have experience or he's not specifically involved with the  
04:22:28 15 listing decisions.

04:22:29 16 MR. KLEIN: Well, right. People who report to  
04:22:31 17 him filed the forms, but he's the person responsible for them.

04:22:37 18 THE COURT: Give me one moment. Other than  
04:22:39 19 2250, do you have any objection to any other exhibits?

04:22:42 20 MS. KEANE: Yes, we also have objection to  
04:22:45 21 DX 2299 which defendants purport to be a summary exhibit.  
04:22:50 22 Again, there is no foundation with this witness to actually  
04:22:54 23 confirm the accuracy of this exhibit or to admit it.

04:23:01 24 THE COURT: Any other objection to any other  
04:23:04 25 exhibits?

04:23:11 1 MS. KEANE: No, Your Honor. I don't believe so.

04:23:15 2 THE COURT: All right. So give me one moment,  
04:23:18 3 please.

04:23:23 4 Thank you, Ms. Keane. I realize I've been  
04:23:26 5 mispronouncing your name. I apologize. You need to correct  
04:23:30 6 me when I'm wrong.

04:23:31 7 All right. So I'll rule on Exhibit 2299 in a  
04:23:38 8 moment, but given that there's an objection to DX 2250, and I  
04:23:43 9 don't recall any question to lay a foundation for admission of  
04:23:47 10 that exhibit, I'm going to give Mr. Klein the opportunity to  
04:23:50 11 do so.

04:23:52 12 And I'm warning counsel going forward we're  
04:23:55 13 proceeding in terms of offering the exhibit each time so that  
04:23:59 14 we don't run into this issue. Why don't you ask Dr. Ketchum  
04:24:04 15 about 2250.

04:24:06 16 MR. KLEIN: Mr. Gross, can you put on DX 2250,  
04:24:10 17 please.

04:24:10 18 BY MR. KLEIN:

04:24:11 19 Q Dr. Ketchum, do you recognize this document?

04:24:13 20 A Is it a single page document?

04:24:17 21 Q No. In fact, may I approach, Your Honor? I'll give the  
04:24:20 22 witness a copy.

04:24:21 23 THE COURT: Yes.

04:24:46 24 THE WITNESS: So the role of my group is to make  
04:24:51 25 the submission of the collated information. We don't prepare



04:24:56 1 the underlying documents, we verify --

04:24:59 2 THE COURT: Dr. Ketchum -- Mr. Klein, please  
04:25:01 3 repeat your question, and that was, I thought, whether he  
04:25:04 4 recognized Exhibit 2250.

04:25:06 5 MR. KLEIN: Correct.

04:25:07 6 THE WITNESS: I recognize that -- the document.

04:25:11 7 BY MR. KLEIN:

04:25:12 8 Q You were in charge of making sure that document was filed  
04:25:15 9 with the FDA?

04:25:16 10 A Yes, we had to push the button to FDA.

04:25:21 11 MR. KLEIN: Okay?

04:25:23 12 MS. KEANE: No, we don't object.

04:25:25 13 THE COURT: I'm sorry, are you withdrawing your  
04:25:28 14 objection?

04:25:28 15 MS. KEANE: Yes, Your Honor.

04:25:29 16 THE COURT: All right. So the only objection  
04:25:31 17 left would be to the demonstrative Exhibit 2299.

04:25:34 18 MR. KLEIN: Right.

04:25:37 19 THE COURT: Is that right?

04:25:38 20 MS. KEANE: Yes, Your Honor, that's correct.

04:25:40 21 Subject to -- we just need to double check the  
04:25:42 22 list of exhibits, but I'm pretty sure otherwise that taking  
04:25:46 23 Mr. Klein's representation that the other exhibits were  
04:25:49 24 actually addressed during the questioning, then, yes, DX 2299.

04:25:55 25 THE COURT: Would you show Exhibit 2299 again,

04:25:58 1 the demonstrative exhibit.

04:26:02 2 So they're just comparing the patent numbers; is  
04:26:05 3 that right?

04:26:06 4 MR. KLEIN: Correct. It's comparing the --  
04:26:09 5 well, the patent information that's submitted to the FDA also  
04:26:13 6 references indications and portions of the label, and this  
04:26:17 7 summary exhibit was designed to prevent going through every  
04:26:22 8 single one of those forms. I think each form is four pages or  
04:26:27 9 so, and there might be a dozen of the forms.

04:26:32 10 And so I don't think there was objection that  
04:26:34 11 the summary exhibit was inaccurate, it was more of a  
04:26:36 12 foundation objection, if I understood it.

04:26:39 13 THE COURT: Ms. Keane, do you want to repeat  
04:26:41 14 your objection?

04:26:42 15 MS. KEANE: Sure.

04:26:42 16 THE COURT: I thought there was some objection  
04:26:45 17 to the accuracy to 2299.

04:26:47 18 MS. KEANE: The objection was, one, as to  
04:26:50 19 foundation and, two, we have not confirmed the accuracy at  
04:26:54 20 this point. And so, given that there's no foundation, we  
04:26:54 21 don't think it should be admitted.

04:26:57 22 MR. KLEIN: Well, but --

04:26:57 23 THE COURT: I thought the foundation was based  
04:26:59 24 on DX 2250.

04:27:01 25 MS. KEANE: Well, that's Mr. Klein's

04:27:03 1 representation, but there's no foundation with Dr. Ketchum  
04:27:06 2 with respect to DX 2299.

04:27:09 3 THE COURT: And, Mr. Klein, that is consistent  
04:27:11 4 with my recollection. You showed the exhibit, then you moved  
04:27:15 5 on to DX 2250, and I don't recall there was any question about  
04:27:21 6 2299.

04:27:22 7 I'm going to permit you the opportunity to do  
04:27:24 8 that, and then I think I have a proposed solution. Do you  
04:27:27 9 want to ask questions about 2299?

04:27:29 10 MR. KLEIN: I think the witness said that he  
04:27:31 11 could not verify it on the stand.

04:27:35 12 THE COURT: So isn't that a basis not to admit  
04:27:38 13 2299?

04:27:39 14 MR. KLEIN: Well, it's still a summary exhibit,  
04:27:41 15 and if the information is accurate, I think it still can be  
04:27:44 16 admitted into evidence based on the underlying information as  
04:27:48 17 long as counsel confirms its accuracy. I think that would be  
04:27:52 18 convenient for the Court.

04:27:52 19 THE COURT: It is a demonstrative exhibit so  
04:27:55 20 it's not admitted as other exhibits.

04:27:59 21 I'm going to defer ruling on the objection to  
04:28:02 22 DX 2299. I'm going to give Ms. Keane the opportunity to  
04:28:07 23 review that exhibit to see if you have any objection.

04:28:10 24 If it's a simple summary, I don't see that it's  
04:28:13 25 objectionable as long as it accurate.

04:28:16 1 So I'm going to give plaintiff's counsel the  
04:28:18 2 opportunity to verify the accuracy of the information. Once  
04:28:21 3 you represent to me it's accurate, then I'll just tell you  
04:28:24 4 what I'm going to do with the exhibit.

04:28:26 5 Other than that, the remaining exhibits that  
04:28:28 6 were identified are admitted, so other than Exhibit 22999.

04:19:31 7 (Defendants' Exhibits 1558, 1800, 1809,  
04:19:36 1814, 1816, 1829, 1836, 1837, 1838,  
04:19:50 8 2104, 2226, 2235, 2241, 2247, 2248,  
04:20:03 2250, 2252, 2255, 2267 received in  
04:28:37 9 evidence.)

04:28:37 10 MS. KEANE: Okay.

04:28:44 11 THE COURT: I have one other concern, Mr. Klein,  
04:28:46 12 and that is -- I know when we started you started on the  
04:28:49 13 cross-examination, you offered to give me a copy of your  
04:28:52 14 demonstrative exhibits.

04:28:54 15 MR. KLEIN: Yes.

04:28:54 16 THE COURT: And I declined. So here's my  
04:28:57 17 concern because there were times when you referenced the  
04:29:00 18 exhibit and you referenced the DDX number --

04:29:03 19 MR. KLEIN: Correct.

04:29:04 20 THE COURT: -- without referencing the actual  
04:29:06 21 page number of the exhibit.

04:29:08 22 So if I don't include your demonstrative, I'm  
04:29:12 23 concerned the record may not be entirely clear what you're  
04:29:16 24 referring to because you didn't identify the page number.

04:29:19 25 MR. KLEIN: I tried to do that, but I certainly

04:29:21 1 may have missed a couple.

04:29:22 2 THE COURT: I think there were times when you  
04:29:24 3 didn't, and I ignored it, because I have the actual exhibit  
04:29:27 4 and I was able to find the information.

04:29:29 5 But as -- towards the end of the  
04:29:32 6 cross-examination I was thinking I would be concerned that for  
04:29:36 7 appellate purposes, I want to make sure the record is clear as  
04:29:40 8 to what you're referring to.

04:29:41 9 So one option is to take your demonstrative and  
04:29:46 10 attach it as an exhibit to the minutes of today's trial so  
04:29:51 11 it's just there in case there's any question about what page  
04:29:56 12 you were referring to.

04:29:57 13 And since all the exhibits are admitted, I don't  
04:29:59 14 know if plaintiff would have any objection to that proposed  
04:30:03 15 solution. If you want to think about it, I'll allow you to do  
04:30:07 16 that as well.

04:30:08 17 MS. KEANE: Yes, Your Honor. Could we take a  
04:30:10 18 moment to confer?

04:30:11 19 THE COURT: So I just need to find a way to have  
04:30:14 20 a record of what DDX 2.63, for example, means. And so you  
04:30:23 21 don't have to decide this today, you can tell me this in the  
04:30:25 22 morning, and I'll find a way to resolve it so I have some  
04:30:28 23 record of what Mr. Klein was referring to.

04:30:31 24 MS. KEANE: Okay. Thank you.

04:30:32 25 MR. KLEIN: Thank you.

04:30:32 1 THE COURT: Thank you.

04:30:54 2 I'm sorry, one more clarification, Mr. Klein.

04:31:06 3 You offered DX 2297 also as demonstrative; is that right?

04:31:11 4 MR. KLEIN: 2297. I don't think so.

04:31:18 5 THE CLERK: Also 2287.

04:31:24 6 THE COURT: I thought you said offered as  
04:31:26 7 demonstrative, I can't remember.

04:31:27 8 MR. KLEIN: These were really for  
04:31:29 9 identification. I think the information got in through the  
04:31:31 10 testimony. These documents we're not moving into evidence.

04:31:34 11 THE COURT: Thank you.

04:31:57 12 MS. KEANE: Your Honor, may I proceed?

04:31:58 13 THE COURT: Yes.

04:31:58 14 REDIRECT EXAMINATION

04:31:58 15 BY MS. KEANE:

04:31:59 16 Q Dr. Ketchum, I just have some follow-up questions for  
04:32:03 17 you. I may jump around a bit so we'll cover a couple of  
04:32:07 18 different topics.

04:32:08 19 One of the things that you talked about with  
04:32:13 20 Mr. Klein was the JELIS study?

04:32:16 21 A Yes.

04:32:16 22 Q Okay. The patients in the JELIS study, the publication  
04:32:24 23 that is -- the JELIS publication is Yokoyama; is that right?

04:32:26 24 A Yes.

04:32:27 25 Q And the patients in Yokoyama are patients with

04:32:31 1 hypercholesterolemia?

04:32:36 2 A Yes, high total cholesterol.

04:32:39 3 Q And how does it the patient population in Yokoyama  
04:32:44 4 compared to the patient population in Amarin's REDUCE-IT  
04:32:49 5 study?

04:32:49 6 A It's very different. So their primary lipid abnormality  
04:32:55 7 is total cholesterol, whereas in REDUCE-IT -- and actually the  
04:33:00 8 patients in JELIS were put on a statin when they started the  
04:33:05 9 study.

04:33:06 10 So in REDUCE-IT, we're talking about patients who  
04:33:09 11 are already on a statin for controlling their bad cholesterol  
04:33:14 12 and who had elevated triglycerides as another lipid  
04:33:17 13 abnormality.

04:33:19 14 Q And did Yokoyama include patients with severe  
04:33:25 15 hypertriglyceridemia?

04:33:26 16 A No, it did not.

04:33:28 17 Q And did the REDUCE-IT study demonstrate cardiovascular  
04:33:35 18 benefits in patients with severe hypertriglyceridemia?

04:33:38 19 A Yes, it did, in patients from all triglyceride levels.

04:33:43 20 Q And that the finding in the REDUCE-IT study with respect  
04:33:49 21 to severe hypertriglyceridemia, that's reflected in Amarin's  
04:33:52 22 updated or revised labeling?

04:33:55 23 A Yes, based on the triglyceride levels in the approved  
04:34:00 24 indication.

04:34:02 25 Q And on the topic of JELIS, you also discussed JELIS with

04:34:16 1 Mr. Klein in the context of FDA's rescission of the ANCHOR  
04:34:25 2 SPA, do you recall that?

04:34:26 3 A Yes, I do.

04:34:27 4 Q And during that discussion you referenced blood levels,  
04:34:30 5 EPA blood levels, I believe?

04:34:33 6 A Yes, plasma levels of EPA.

04:34:36 7 Q And that was a comparison of blood levels from patients  
04:34:43 8 who participated in the JELIS study versus patients in the  
04:34:46 9 Amarin studies; is that right?

04:34:48 10 A Yes, a so-called cross study comparison, meaning we  
04:34:52 11 didn't have access to the samples from JELIS so we had to  
04:34:56 12 compare to their published information.

04:34:59 13 Q And where -- where was the information that Amarin had to  
04:35:03 14 compare that -- those blood levels, where did that come from?

04:35:07 15 A It came from a follow-on publication from the JELIS study  
04:35:12 16 group.

04:35:12 17 Q And how about the blood levels with respect to Amarin  
04:35:16 18 studies, where did that come from?

04:35:19 19 A It came from an Amarin directed publication.

04:35:22 20 Q Were there particular Amarin studies that were underlying  
04:35:25 21 that information?

04:35:26 22 A Both MARINE and ANCHOR.

04:35:31 23 Q And the published data that you referred to with the  
04:35:35 24 blood levels from the JELIS study, do you recall when that  
04:35:40 25 information was made available, when it was published?



04:35:43 1 A Some years after the Yokoyama publication. I do not  
04:35:48 2 remember the precise date.

04:35:50 3 Q Another topic that you discussed with Mr. Klein was the  
04:36:21 4 Mori reference, do you recall that?

04:36:23 5 A Yes.

04:36:25 6 MS. KEANE: And if we could take a look at --  
04:36:30 7 we'll use -- I believe it's Defendants' Exhibit Number 1538,  
04:36:39 8 and if we could turn to page ending n 006.

04:36:48 9 And, Mr. Brooks, could you pull up the second  
04:36:51 10 column on page -- I think it's 006. Actually, I think it's --  
04:37:10 11 this should be -- is this DX 1538? Okay. If we could go to  
04:37:18 12 page 6. And then if we can pull up the full paragraph in the  
04:37:29 13 second column starting "although."

04:37:29 14 BY MS. KEANE:

04:37:35 15 Q And the statement there in -- on page 6 states that,  
04:37:39 16 "Although the LDL-C" -- or,

04:37:42 17 "Although the LDL-cholesterol concentration  
04:37:45 18 increased after EPA and DHA intakes, the increase was  
04:37:49 19 significant only after DHA."

04:37:51 20 Do you see that?

04:37:51 21 A Yes, I see those words.

04:37:53 22 Q And so it's the case that in Mori the LDL-C levels  
04:37:59 23 increased after the administration of EPA as well?

04:38:05 24 A It increased, yes. It increased after taking both EPA  
04:38:13 25 and DHA.

04:38:14 1 Q If we could take a look at Table 2 on page 4, and Table  
04:38:27 2 2, the third row down refers to LDL cholesterol. Do you see  
04:38:34 3 That?

04:38:34 4 A Yes, I do.

04:38:34 5 Q In this row, is that reporting the data on LDL  
04:38:39 6 cholesterol?

04:38:40 7 A Yes.

04:38:41 8 Q And that includes the data from the placebo EPA and DHA  
04:38:46 9 as well?

04:38:47 10 A Yes.

04:38:47 11 Q And, again, that shows an increase in LDL-C after  
04:38:52 12 administration of EPA?

04:38:54 13 A Yes. In the far right-hand column it shows increases in  
04:38:58 14 both EPA and DHA.

04:39:00 15 Q If you see at the top of Table 2, the reference refers  
04:39:06 16 to -- under the EPA heading, there's an N of 19? Do you see  
04:39:12 17 that?

04:39:12 18 A Yes.

04:39:15 19 Q What does that N of 19 refer to?

04:39:15 20 A That's 19 samples or patients in that treatment group.

04:39:20 21 Q And how many patients were in the DHA treatment group?

04:39:24 22 A Seventeen.

04:39:25 23 Q And how -- do you consider the sizes of the -- the sample  
04:39:37 24 sizes in the study to be large samples?

04:39:40 25 A No, they're small.

04:39:43 1 Q In addition, I think when you discussing the Mori  
04:39:47 2 article, so DX 1539, with Mr. Klein, there was more  
04:39:53 3 information that you wanted to convey about the Mori article  
04:39:56 4 in response to one of his questions?

04:39:58 5 A Within the author's conclusions at the end of the article  
04:40:03 6 in the last paragraph.

04:40:05 7 Q Are you referring to page -- the page ending in 8?

04:40:09 8 A The page ending in 8.

04:40:15 9 Q And what is it that you were referring to?

04:40:18 10 A I'm referring to the entire paragraph that's trying to  
04:40:23 11 sum up the author's findings in this study, that they suggest  
04:40:27 12 that despite an increase in LDL cholesterol after DHA  
04:40:34 13 supplementation, that it may represent a more favorable lipid  
04:40:39 14 profile than that seen after EPA supplementation. So, if  
04:40:48 15 anything, it was pointing to DHA rather than EPA.

04:40:52 16 Q And when you say you're referring to the authors --

04:40:55 17 A The authors, Mori, et al.

04:41:10 18 Q Do you recall you were also --

04:41:12 19 MS. KEANE: Mr. Brooks, you can take down the  
04:41:13 20 screen, thank you.

04:41:13 21 BY MS. KEANE:

04:41:15 22 Q Do you recall that you were also shown a number of -- or  
04:41:18 23 a few internal documents from Amarin from the 2008 time  
04:41:22 24 period?

04:41:22 25 A Yes.

04:41:23 1 Q And specifically, those were Defendants' Exhibits 1814  
04:41:30 2 and 1829?

04:41:31 3 A Yes.

04:41:32 4 Q And there were no authors listed on the documents that  
04:41:38 5 you reviewed; is that right?

04:41:39 6 A That's correct.

04:41:41 7 Q And I think you discussed with Mr. Klein that your  
04:41:48 8 understanding is the documents were from the 2008 time frame;  
04:41:52 9 is that right?

04:41:53 10 A Yes.

04:41:53 11 Q How large of a company was Amarin back in 2008?

04:41:59 12 A It was maybe marginally beyond a dozen employees at that  
04:42:06 13 stage.

04:42:06 14 Q So it was a small company?

04:42:08 15 A Very small company.

04:42:09 16 Q And, to your knowledge, did the individuals who are named  
04:42:15 17 as inventors on the patents, would they, you know, regularly  
04:42:20 18 communicate with their colleagues?

04:42:22 19 A Yes, they would.

04:42:23 20 MR. KLEIN: Objection, foundation. I think the  
04:42:26 21 question is directed to the 2008 time frame which was four  
04:42:30 22 years before Dr. Ketchum joined the company.

04:42:34 23 THE COURT: Would you lay some additional --  
04:42:37 24 clarify the time frame of your question.

04:42:39 25 MS. KEANE: Sure, and I'll rephrase the

04:42:41 1 question.

04:42:41 2 BY MS. KEANE:

04:42:42 3 Q Based on the documents, is there any indication that  
04:42:46 4 other employees at Amarin were not also involved in the  
04:42:51 5 discussions that are reflected in those documents?

04:42:55 6 MR. KLEIN: Objection. Calls for speculation.

04:42:56 7 MS. KEANE: Your Honor, Mr. Klein just crossed  
04:42:58 8 him on these exhibits extensively and asked him a lot of  
04:43:03 9 information about these documents.

04:43:05 10 To the extent -- to the extent that Dr. Ketchum  
04:43:09 11 has foundation to speak to the documents in 2008 on cross, I  
04:43:13 12 think he has foundation to respond to that now.

04:43:15 13 THE COURT: But the objection is that you're  
04:43:17 14 asking for information that's outside of these documents.  
04:43:20 15 You're asking whether he knew that the staff at the time in  
04:43:23 16 2008 before he joined Amarin were conferring.

04:43:26 17 MS. KEANE: No, my question, Your Honor, right  
04:43:28 18 now, is based on the documents.

04:43:30 19 THE COURT: Based on what documents?

04:43:32 20 MS. KEANE: So if we could turn to Defendants'  
04:43:36 21 Exhibits 1814, and, on the other hand, I can clarify my  
04:43:49 22 questions if --

04:43:50 23 THE COURT: Yes.

04:43:50 24 BY MS. KEANE:

04:43:51 25 Q Okay. So, Dr. Ketchum, Defendants' Exhibit 1814 is a

04:43:56 1 document that you discussed earlier with Mr. Klein. Do you  
04:43:59 2 recall that?

04:43:59 3 A Yes.

04:44:00 4 Q And one of the things that you discussed with Mr. Klein  
04:44:05 5 are various statements that are contained within the document?

04:44:07 6 A Yes.

04:44:08 7 Q Can you tell from the document who the author of the  
04:44:13 8 document was?

04:44:14 9 A No. The author's name is not listed on the front of the  
04:44:19 10 document.

04:44:19 11 Q Okay. And, to your knowledge, as of the date that is  
04:44:24 12 listed on the document, March 10th, 2008, were any of the  
04:44:29 13 inventors of the patents employees of Amarin?

04:44:32 14 A Yes, they were.

04:44:33 15 Q And at that point in time the size of the company was  
04:44:38 16 small, approximately 12 people?

04:44:40 17 A Yes.

04:44:40 18 Q So as far as -- with respect to the documents, do you  
04:44:59 19 have -- is it your understanding that it's possible that the  
04:45:01 20 documents reflect the views of multiple people?

04:45:03 21 MR. KLEIN: Objection. Calls for speculation.  
04:45:05 22 Lack of foundation.

04:45:07 23 THE COURT: So the -- would you state your  
04:45:09 24 question again?

04:45:10 25 MS. KEANE: Sure. The question is based on the

04:45:12 1 document, do you have -- based on the document, is it possible  
04:45:15 2 the document reflects the views of multiple people.

04:45:18 3 THE COURT: And the objection is speculation; is  
04:45:19 4 that right?

04:45:20 5 MR. KLEIN: Yes.

04:45:20 6 THE COURT: The objection is sustained.

04:45:39 7 And I would explain that because the question  
04:45:41 8 asked for whether -- a possibility as to whether it reflected  
04:45:44 9 views of multiple people, that is a quintessential speculation  
04:45:51 10 question.

04:45:53 11 BY MS. KEANE:

04:46:25 12 Q If we could turn to Defendants' Exhibit -- I'm going to  
04:46:39 13 go back to -- actually, if we could stay with Exhibit 1814.

04:46:48 14 Is there anything in the document that indicates  
04:46:52 15 that the contents of any of the statements in the document did  
04:46:57 16 not come from any of the 12 people employed by Amarin at that  
04:47:03 17 point in time?

04:47:07 18 A No.

04:47:08 19 Q If we could go to --

04:47:11 20 MS. KEANE: I don't know if it's possible to go  
04:47:14 21 to defendants' demonstrative 2.19. Would it be possible to  
04:47:19 22 pull that up?

04:47:30 23 COMPUTER TECHNICIAN: Switch back over?

04:47:32 24 MS. KEANE: Two point --

04:47:34 25 THE COURT: I'm sorry, what's the number again?

04:47:36 1 MS. KEANE: This is from defendants'  
04:47:37 2 demonstratives, it's DDX 2.19, and the document that is  
04:47:44 3 referred to in the document is Defendants' Exhibit 1814.  
04:47:56 4 We're going to take a look at page 10.

04:47:56 5 BY MS. KEANE:

04:48:02 6 Q Dr. Ketchum, do you recall that you discussed the  
04:48:04 7 highlighted statement on page 10 with Mr. Klein?

04:48:07 8 A Yes.

04:48:08 9 Q Okay. You state that,

04:48:10 10 "Amarin does not believe there is a need to  
04:48:13 11 conduct any additional pharmacokinetic drug  
04:48:18 12 interaction or other studies."

04:48:21 13 A Yes.

04:48:21 14 Q And as of 2008, I believe you testified earlier that  
04:48:27 15 Amarin had conducted its own CNS studies; is that right?

04:48:32 16 A Yes.

04:48:33 17 Q And so are the studies that are referenced on DX 1814 on  
04:48:41 18 page 10, are those referring to internal Amarin studies?

04:48:48 19 A Still in the context of the highlighted sentence?

04:48:53 20 Q Yes. Well, let me rephrase the question.

04:48:55 21 At the time of this statement did Amarin have its  
04:48:58 22 own pharmacokinetic and drug interaction studies?

04:49:03 23 A Not in support of the indication for severe  
04:49:06 24 hypertriglyceridemia.

04:49:06 25 Q Did it have those studies with respect to CNS



04:49:10 1 indications?

04:49:11 2 A It had some other clinical development information that  
04:49:14 3 was required for the Huntington's disease submissions.

04:49:18 4 Q And at that point in time Amarin had its own internal  
04:49:22 5 data?

04:49:22 6 A It had, certainly, internal data on a number of clinical  
04:49:28 7 pharmacology studies, including dose range finding in some  
04:49:35 8 other disease areas.

04:49:40 9 MS. KEANE: If we could turn to defendants'  
04:49:43 10 demonstrative 2.56. Would it be possible to pull up  
04:50:12 11 defendants' -- oh, thank you very much.

04:50:12 12 BY MS. KEANE:

04:50:15 13 Q And the document cited here is Defendants' Exhibit 1816  
04:50:20 14 on page 85. And do you recall, Dr. Ketchum, that during --  
04:50:30 15 that you discussed with Mr. Klein the sentences that are  
04:50:34 16 highlighted on the page?

04:50:37 17 A Yes.

04:50:37 18 Q And do you recall the date of this document?

04:50:43 19 A The date of this document is June 16th, 2008.

04:50:48 20 Q And I want to direct your attention to the sentence  
04:50:52 21 that's not highlighted after the last sentence, the last  
04:50:56 22 highlighted sentence on DDX 2.56, and you see there's a  
04:51:01 23 statement there that says,

04:51:03 24 "However, there have been no controlled  
04:51:05 25 studies of highly purified ethyl-EPA in patients with

04:51:10 1 severe hypertriglyceridemia, the group must  
04:51:11 2 susceptible to marked rises in LDL cholesterol  
04:51:16 3 induced by Lovaza."

04:51:16 4 A Yes.

04:51:17 5 Q And that is information that Amarin provided to FDA in  
04:51:23 6 the document that is DX 1816?

04:51:28 7 A Yes, that's correct.

04:51:50 8 Q Dr. Ketchum, one of the things that you -- you also  
04:51:52 9 referenced Omacor during your testimony?

04:51:56 10 A Yes.

04:51:57 11 Q And Omacor is now known as Lovaza?

04:52:02 12 A That's correct, in the United States.

04:52:04 13 Q Is Lovaza approved as a fixed dose combination of EPA and  
04:52:10 14 DHA?

04:52:10 15 A It's approved as an omega-3 acid ethyl esters that  
04:52:21 16 includes EPA and DHA is the predominant omega-3 species, yes.

04:52:21 17 Q Well, and what does that mean that it includes other  
04:52:27 18 omega three species?

04:52:28 19 A It means that the two major peaks, if you look at this on  
04:52:36 20 a particular instrument, are EPA and DHA, but that there are  
04:52:40 21 other omega-3s and omega-6s that can be in that product.

04:52:48 22 Q And when you were at -- you were at Reliant and then GSK  
04:52:59 23 in the 2005-2008 time frame?

04:53:01 24 A Yes, that's correct.

04:53:03 25 Q And when you were at Reliant and GSK, what was your view

04:53:07 1 of purified EPA?

04:53:10 2 A We were not --

04:53:12 3 MR. KLEIN: Objection. This is going beyond the  
04:53:14 4 scope of my cross. I didn't say ask any questions along these  
04:53:19 5 lines.

04:53:19 6 MS. KEANE: Your Honor, I think Mr. Klein asked  
04:53:22 7 a number of questions about what was known about DHA and EPA  
04:53:27 8 back in the time frame of 2008 in various different  
04:53:27 9 references.

04:53:33 10 MR. KLEIN: I didn't ask any questions about his  
04:53:35 11 work at GSK.

04:53:39 12 MS. KEANE: And, to be clear, I'm not asking  
04:53:41 13 specifically for his work, I'm just asking for his  
04:53:42 14 understanding.

04:53:43 15 THE COURT: You're saying that you get to ask  
04:53:45 16 him about his time at Reliant because on cross-examination  
04:53:49 17 there were questions about the 2008 time period?

04:53:52 18 MS. KEANE: I'm just trying to understand -- I'm  
04:53:55 19 just trying to ask him for more information about what was  
04:53:58 20 understood about purified EPA back in 2008 which is in  
04:53:58 21 response to Mr. Klein's questions about what references  
04:54:07 22 conveyed about EPA and DHA back in --

04:54:07 23 MR. KLEIN: That's also calling for expert  
04:54:10 24 testimony then. I was asking factual questions about what  
04:54:13 25 documents say. I didn't ask him for any expert testimony.

04:54:17 1 MS. KEANE: Your Honor, I think Mr. Klein's  
04:54:20 2 questioning, to be fair, went -- we gave him leeway with the  
04:54:23 3 questions, but they went beyond questions just asking for  
04:54:29 4 recitation of what's in the document.

04:54:30 5 THE COURT: Well, so on direct examination  
04:54:34 6 Dr. Ketchum testified extensively about kind of what existed  
04:54:38 7 before in terms of in the scientific community and in the drug  
04:54:45 8 environment, what was available.

04:54:46 9 But I don't recall that those questions were  
04:54:48 10 asked on cross-examination, and certainly there were no  
04:54:51 11 questions related to his time at other companies.

04:54:55 12 So on that basis I sustain the objection unless  
04:54:58 13 you have an another reason how you can ask him questions that  
04:55:02 14 exceed the scope of the cross-examination.

04:55:05 15 MS. KEANE: Your Honor, I can -- I'll withdraw  
04:55:08 16 the question and I'll ask a different question.

04:55:11 17 BY MS. KEANE:

04:55:27 18 Q Dr. Ketchum, once you -- once you joined Amarin, did you  
04:55:31 19 understand Amarin's views of the benefits of purified EPA to  
04:55:37 20 differ than other views in the field?

04:55:43 21 MR. KLEIN: Objection to form. I don't  
04:55:44 22 understand the question.

04:55:46 23 THE COURT: Well --

04:55:47 24 MS. KEANE: I'll rephrase the question.

25 ///

04:55:49 1 BY MS. KEANE:

04:55:50 2 Q Dr. Ketchum, when you joined Amarin, what were Amarin's  
04:55:54 3 views of purified EPA?

04:55:56 4 A So Amarin had deeply-held beliefs and confidence in  
04:56:03 5 progressing a program. By that point in time, both the MARINE  
04:56:08 6 and ANCHOR trial results had read out by the time I joined in  
04:56:13 7 February of 2012.

04:56:16 8 Q And since you have been at Amarin, is it your view that  
04:56:25 9 Amarin's view of the clinical benefit the purified EPA are  
04:56:30 10 different than those outside of Amarin?

04:56:31 11 A Yes.

04:56:31 12 THE COURT: I'm sorry, you're asking for his  
04:56:34 13 view as to what Amarin's view is?

04:56:36 14 MS. KEANE: I'm sorry, I'm asking for -- whether  
04:56:39 15 you have an understanding as to Amarin's view compares to  
04:56:44 16 others in the field.

04:56:45 17 MR. KLEIN: I have a number of objections,  
04:56:48 18 foundation, speculation, hearsay.

04:56:51 19 He was a 30(b)(6) witness which allows us to  
04:56:54 20 question him on behalf of Amarin, but I don't think plaintiffs  
04:56:59 21 can ask him to answer questions on behalf of Amarin generally.  
04:57:04 22 If it includes hearsay, it's speculation.

04:57:08 23 THE COURT: Well, the question is whether he has  
04:57:10 24 an understanding that Amarin has a different view than all the  
04:57:14 25 views outside of Amarin? Is that the gist of the question?

04:57:19 1 MS. KEANE: Yes. My question is really how  
04:57:22 2 Amarin's views differ than others that are in the field for --  
04:57:27 3 others in the field.

04:57:28 4 THE COURT: But doesn't that require him to  
04:57:31 5 identify all the views that are in the field as to what they  
04:57:34 6 are before he compares them to Amarin?

04:57:37 7 I agree. I have a problem with the question  
04:57:39 8 given it also seems to exceed the scope of this trial as well.

04:57:43 9 I know that prior art -- there's a lot of  
04:57:44 10 discussions about the prior arts, and so if you can ground it  
04:57:47 11 in the studies that have been introduced, but then that will  
04:57:49 12 be repetitive of what's already testified to.

04:57:54 13 MS. KEANE: Understood, Your Honor. I'll  
04:57:56 14 withdraw the question.

04:57:57 15 BY MS. KEANE:

04:58:15 16 Q Dr. Ketchum, in light of Amarin's results with the  
04:58:21 17 REDUCE-IT study, what are Amarin's -- since the REDUCE-IT  
04:58:27 18 study has been completed, what is your view of the JELIS  
04:58:32 19 study?

04:58:34 20 A They have been kind of touched upon in some of the other  
04:58:43 21 documents. There's some limitations to the JELIS study.

04:58:47 22 I think one key difference between JELIS and  
04:58:50 23 REDUCE-IT is, as I mentioned earlier, that shortly after the  
04:58:55 24 *New England Journal of Medicine* publication of the REDUCE-IT  
04:58:58 25 results, that there was this broad and rapid acceptance of the

04:59:04 1 REDUCE-IT results, in medical society guidelines, that even up  
04:59:07 2 to that point in time that had never happened with the JELIS  
04:59:11 3 study results. So that's -- that would be my overarching  
04:59:17 4 view.

04:59:54 5 MS. KEANE: Your Honor, I have no further  
04:59:57 6 questions at this time.

04:59:58 7 THE COURT: Thank you.

05:00:02 8 Mr. Klein, do you have any brief redirect?

05:00:05 9 MR. KLEIN: I do not.

05:00:05 10 THE COURT: I mean, recross, I'm sorry.

05:00:05 11 MR. KLEIN: I don't --

05:00:07 12 THE COURT: You do not either way, no redirect  
05:00:09 13 or recross.

05:00:09 14 MR. KLEIN: Either one, yes.

05:00:10 15 THE COURT: All right. Dr. Ketchum, you may be  
05:00:12 16 excused.

05:00:14 17 THE WITNESS: Thank you.

05:00:14 18 (The witness was excused.)

05:00:25 19 THE COURT: I know I indicated that each day we  
05:00:27 20 would recess at 5:30. For today, there was an evidentiary --  
05:00:32 21 there was some issue with the exhibits that were identified  
05:00:34 22 earlier. I wonder if it would make sense for me to resolve  
05:00:39 23 that objection instead of having Amarin call its next witness.  
05:00:42 24 I don't know how long it would take to resolve that objection.

05:00:50 25 MS. WHITT: Thank you, Your Honor.

05:00:59 1 As I mentioned this morning, on Saturday night  
05:01:01 2 we were served a new exhibit list that added 29 new exhibits.  
05:01:06 3 As you know, we -- under your order regarding, trial we were  
05:01:11 4 required to submit our final exhibit list on Monday,  
05:01:15 5 January 6, and then we got these 48 hours before the beginning  
05:01:20 6 of trial.

05:01:20 7 We did not object to two because they were very  
05:01:22 8 recently created documents so recently available. It came up  
05:01:27 9 during Mr. Klein's cross-examination, that was one the  
05:01:31 10 documents on this list, so we're not objecting to those two  
05:01:34 11 that were recently added, it's the remaining 27 on the list  
05:01:37 12 that have been in defendants' possession for quite some time.

05:01:47 13 THE COURT: So the exhibit list that was filed  
05:01:49 14 before trial ended at 2265, and earlier I admitted 2267 and --  
05:01:56 15 well, 2299 I'm deferring ruling on.

05:02:00 16 Are those the two exhibits that you reference  
05:02:01 17 that there are is no objection to?

05:02:05 18 MS. WHITT: There's also a 2266 on the updated  
05:02:07 19 exhibit list that we were served. I think that that's not yet  
05:02:12 20 on the version that the Court has.

05:02:14 21 THE COURT: My version ends at 2265, and I don't  
05:02:18 22 recall hearing that 2266 was offered yet.

05:02:22 23 MS. WHITT: 2266 is, like I said, is on the  
05:02:24 24 version that the defendants' gave us on Saturday night, and  
05:02:27 25 it's a new document that was created recently.



05:02:30 1 THE COURT: I'm sorry. So of the 29 new  
05:02:34 2 exhibits that were added as of Saturday night, plaintiff does  
05:02:38 3 not object to two of them which are what number again?

05:02:41 4 MS. WHITT: 2266 and 2267.

05:02:45 5 THE COURT: Because they were new documents or  
05:02:49 6 based on information recently produced or created?

05:02:54 7 MS. WHITT: Yeah, that's right. They recently  
05:02:56 8 became available.

05:02:57 9 It's also my understanding from our meet and  
05:03:00 10 confer last night that the defendants have withdrawn two of  
05:03:03 11 these exhibits, but that leaves the 25 additional exhibits.

05:03:07 12 THE COURT: Let me hear from defendant as to the  
05:03:09 13 reason for the late disclosure.

05:03:16 14 MR. ROUNDS: Your Honor, good afternoon.  
05:03:20 15 Michael Rounds for the Dr. Reddy's defendants.

05:03:20 16 As the Court knows, approximately 2,000 exhibits  
05:03:24 17 have been marked by the parties in this case.

05:03:27 18 These came up when my colleague Connie Huttner  
05:03:30 19 and I were preparing for two of the experts that defendants  
05:03:33 20 have in this case, specifically, Dr. Mason and Dr. Ismail. We  
05:03:38 21 discovered these documents as we were preparing for their  
05:03:42 22 cross-examination.

05:03:43 23 THE COURT: Well, you discovered them, but they  
05:03:45 24 have been produced --

05:03:47 25 MR. ROUNDS: That's true. That's true.

05:03:49 1 THE COURT: -- all along.

05:03:50 2 MR. ROUNDS: That's true.

05:03:51 3 THE COURT: So it hasn't been a recent discovery  
05:03:53 4 technically.

05:03:54 5 MR. ROUNDS: No, no. So we merely disclosed  
05:03:57 6 them as exhibits to the other side.

05:03:59 7 The real thing here, Your Honor, is there's no  
05:04:02 8 prejudice. These witnesses aren't going to testify for  
05:04:05 9 another two weeks in all likelihood.

05:04:07 10 So they know the exact exhibits that we've  
05:04:10 11 identified for these experts. There's no prejudice here  
05:04:14 12 whatsoever.

05:04:15 13 And I would point out --

05:04:16 14 THE COURT: Is the reason -- just because the  
05:04:18 15 witnesses are not expected to testify in a couple of weeks  
05:04:21 16 doesn't excuse the late disclosure. There's a reason why I  
05:04:26 17 have these orders about when exhibits are to be produced so  
05:04:30 18 there's no surprise to the other side.

05:04:33 19 So the defendants' reason for the late  
05:04:35 20 disclosure is we realized we need these exhibits when we  
05:04:39 21 started to prepare for the cross-examination of experts.

05:04:44 22 MR. ROUNDS: Yes, they were inadvertently not  
05:04:47 23 included in the Pretrial Order in the exhibit list, that's  
05:04:50 24 true.

05:04:50 25 THE COURT: All right. Let me hear from the

05:04:52 1 plaintiff then given that that's the explanation as to why the  
05:04:57 2 Court should exclude them.

05:04:58 3 MR. ROUNDS: Your Honor, one other point is that  
05:05:00 4 these things happen during trial. So, for example --

05:05:03 5 THE COURT: These things happen, but not 27 new  
05:05:07 6 exhibits.

05:05:07 7 MR. ROUNDS: Well, so Dr. Nicholson, who they  
05:05:10 8 have identified as an expert on the issue of commercial  
05:05:13 9 success, he was not listed in the pretrial order as witness.  
05:05:17 10 We didn't take issue with that. We know about him.

05:05:20 11 They know about these documents. It's their  
05:05:22 12 documents. Of course, they know about them. There's no  
05:05:25 13 prejudice to allow us to use these in two weeks.

05:05:28 14 THE COURT: All right. So all the documents  
05:05:29 15 that -- so now I understand there's 27 new total, they don't  
05:05:35 16 object to two of them, so 25 new exhibits, and you're saying  
05:05:38 17 all these 25 exhibits are plaintiff's documents?

05:05:42 18 MR. ROUNDS: Yes, they are. They're all Amarin  
05:05:44 19 documents, they're e-mails and then some prior art.

05:05:47 20 THE COURT: All right.

05:05:53 21 MS. WHITT: It's true that they are Amarin  
05:05:58 22 documents. They were produced almost three years ago pursuant  
05:06:03 23 to --

05:06:03 24 THE COURT: Which probably explains why they  
05:06:06 25 hadn't thought to look at them.

05:06:07 1 So the real question is what would be the  
05:06:10 2 prejudice to Amarin if I were to allow the late disclosure  
05:06:16 3 documents to be used given that they're Amarin documents and  
05:06:20 4 that, as Mr. Rounds represents, these witnesses are not  
05:06:25 5 expected to testify until the second week of the trial?

05:06:29 6 MS. WHITT: I'm not sure that that's correct --  
05:06:31 7 I don't know if that's correct.

05:06:33 8 THE COURT: Which part do you not know?

05:06:35 9 MS. WHITT: I don't know if it's correct that  
05:06:38 10 they won't testify until two weeks from now.

05:06:40 11 I will say that, you know, we have pretrial  
05:06:43 12 exchanges to avoid these late disclosures and avoid the burden  
05:06:48 13 of viewing of these exhibits and creating -- preserving  
05:06:48 14 objections to them.

05:06:52 15 We exchanged our initial exhibit list back in  
05:06:54 16 November, on, I believe, November 11, under a stipulation  
05:06:57 17 between the parties. I think that's docket entry 280, and so  
05:07:01 18 we had that agreement. So we had that initial exchange.

05:07:05 19 There have been numerous amendments to that  
05:07:08 20 exhibit list between that November 11th date and January 6th,  
05:07:12 21 and the point is there has to be a line somewhere to avoid the  
05:07:18 22 burden of reviewing these exhibits and objecting to them and  
05:07:22 23 meeting and conferring on them, and that seems to have passed.

05:07:28 24 THE COURT: I agree that there -- this is a  
05:07:31 25 reason why there are deadlines that are set.

05:07:33 1 This is what I'm going to do. I'm going to  
05:07:36 2 require the defendants, for the 25 new exhibits that were  
05:07:40 3 disclosed to which there's objection, to identify the witness  
05:07:44 4 that you plan to use -- the witness for which you plan to  
05:07:51 5 use the cross -- the witness you plan to cross-examine  
05:07:56 6 those -- let me see if I can say this better. It's end of the  
05:07:58 7 day, I'm sorry.

05:07:59 8 My plan is that you have to identify which  
05:08:02 9 witnesses you plan to use these new documents for, and I would  
05:08:05 10 like -- because they were not given to me, I don't know how  
05:08:08 11 many pages are -- how many pages are involved in each of the  
05:08:12 12 exhibits.

05:08:13 13 Certainly, if each one -- one, the reason that I  
05:08:17 14 would allow for them to be admitted or offered, anyways, is  
05:08:23 15 the fact that they're Amarin's documents, but I also agree  
05:08:27 16 that if these documents are extensive, I would be concerned  
05:08:31 17 about counsel's ability to prepare these witnesses for trial.

05:08:35 18 So for me to decide whether or not I'm going to  
05:08:39 19 accept of lack of prejudice argument, I need to see the  
05:08:42 20 documents, one.

05:08:44 21 Two, to alleviate any argument that Amarin now  
05:08:48 22 has less time to prepare for those documents to be offered,  
05:08:52 23 I'm going to require that defendants' counsel identify the  
05:08:56 24 witnesses they plan to use these documents for, and that  
05:09:00 25 should be done by tomorrow, and then I would like to see the

documents tomorrow so hopefully at the end of the day I'll have a ruling for you on the documents.

Peggie will also tell you that whenever you update the exhibit list you're supposed to file them on the docket and give her and I a copy, and the reason I'm very particular about how exhibits are offered is I am taking notes so that I can check what exhibits have been admitted for the record. Peggie is doing the same thing.

And earlier I noticed that there were some -- so I'm juggling several lists here. I'm looking at the stipulated list of exhibits, I'm looking at the parties' list of exhibits. I've marked them so I can make sure I can identify what's been admitted which is why I want to make sure that this is kind of easy for me to do as well.

So going forward, the exhibits will be offered at the time they're introduced so I can mark them so I decide -- so I can easily verify whether they've been admitted.

Is there anything else? Did I sort of resolve the issue with exhibits?

MS. WHITT: Yes, thank you, Your Honor.

Since we have a little more time today, I thought it might make sense to also offer the deposition designations that plaintiffs want to offer at this point.

So we have -- as Mr. Sipes mentioned this

05:10:17 1 morning, we have reached an agreement where we provide the  
05:10:19 2 Court with the page and line number. We have those on flash  
05:10:23 3 drives for the Court, and then I just need to move in the  
05:10:26 4 exhibits that are referenced in those page and line numbers.

05:10:30 5 THE COURT: And what are those exhibits?

05:10:35 6 MS. WHITT: Those exhibits are trial exhibits.  
05:10:38 7 I'll go slow; 291, 292 --

05:10:39 8 THE COURT: I'm sorry, are these all plaintiffs'  
05:10:41 9 exhibits?

05:10:43 10 MS. WHITT: Yes.

05:10:43 11 THE COURT: PX?

05:10:43 12 MS. WHITT: Yes.

05:10:43 13 THE COURT: All right. I know that there's an  
05:10:46 14 ending number but I don't remember what it is. It would be  
05:10:49 15 easier if I start out with -- so PX291?

05:10:53 16 MS. WHITT: Yes, 291, 292, 307, 294, 308, 273,  
05:11:03 17 185, 186 --

05:11:07 18 THE COURT: So hang on. Slow down just one  
05:11:09 19 moment, I'm sorry.

05:11:11 20 MS. WHITT: My apologies.

05:11:11 21 THE COURT: My Surface doesn't react as fast as  
05:11:15 22 your -- the speed at which you're talking. So I ended at 308.

05:11:20 23 MS. WHITT: 308, 273, 185, 186, 198, 196, 273,  
05:11:40 24 193, 192, 195, 187, 188, 194, 274, 189, 190, 821, 815, 817,  
05:12:08 25 818, 816, 813, 819, 814, 820, 812, 219, 21, 226, 227, 210,

05:12:36 1 216, 217, 219, 228, 208, 206, 207, 203, 479, 935, 753, 755,  
05:13:07 2 757, 754, 479, 480, 474, 475, 472, 476, 469 and 470.

05:13:36 3 That's it.

05:13:37 4 THE COURT: Any objection to those exhibits  
05:13:40 5 being admitted?

05:13:41 6 MR. KLEIN: No objection.

05:13:42 7 THE COURT: All right. Then the exhibits that  
05:13:43 8 have been identified are admitted, and I will accept the flash  
05:13:48 9 drive of the deposition testimony.

05:10:53 10 (Plaintiffs' Exhibits 291, 292, 307, 294,  
05:10:58 308, 273, 185, 186, 198, 196, 273, 193,  
05:11:41 11 192, 195, 187, 188, 194, 274, 189, 190,  
05:12:01 821, 815, 817, 818, 816, 813, 819, 814,  
05:12:18 12 820, 812, 219, 21, 226, 227, 210, 216,  
05:12:37 217, 219, 228, 208, 206, 207, 203, 479,  
05:12:58 13 935, 753, 755, 757, 754, 479, 480, 474,  
05:13:20 475, 472, 476, 469 and 470 received in  
05:13:50 14 evidence.)

05:13:50 15 MS. WHITT: May I approach?

05:13:53 16 THE COURT: Thank you.

05:14:00 17 MS. HUTTNER: I'm sorry, Your Honor, just to be  
05:14:01 18 clear the exhibit that was submitted is both the designations  
05:14:04 19 and counterdesignations from the defendants.

05:14:07 20 MS. WHITT: That's correct.

05:14:08 21 THE COURT: I don't know, I just wrote down the  
05:14:10 22 exhibit numbers.

05:14:11 23 MS. WHITT: That is correct.

05:14:12 24 I believe that that flash drive -- because we  
05:14:14 25 were intending -- we thought we might get to Dr. -- our next



05:14:17 1 witness' testimony, that flash drive also includes an  
05:14:20 2 electronic version of his demonstrative slides so it will be  
05:14:26 3 for the Court's convenience. It also contains a copy of the  
05:14:30 4 opening slides that were used by plaintiffs.

05:14:32 5 THE COURT: How is it identified on the flash  
05:14:32 6 drive?

05:14:34 7 MS. WHITT: I believe it's identified by file  
05:14:38 8 name, but I'll have to confirm.

05:14:40 9 THE COURT: Yes, because I'm going to have the  
05:14:42 10 exhibits that we use tomorrow downloaded to my external hard  
05:14:46 11 drive so I have access to them, so I just need to know what is  
05:14:50 12 so that the Court's IT staff can do it for me.

05:14:54 13 MS. WHITT: Sure. And if it's at all an  
05:14:57 14 inconvenience, we can provide a different flash drive that  
05:14:58 15 just has these deposition designations. We were just trying  
05:14:58 16 to --

05:14:59 17 THE COURT: They probably would prefer to have  
05:15:01 18 it tonight as opposed to tomorrow.

05:15:05 19 MS. WHITT: Okay. Thank you.

05:15:05 20 THE CLERK: Counsel, your flash drive has a  
05:15:09 21 password to it?

05:15:10 22 MS. WHITT: Oh.

05:15:13 23 THE COURT: You should write it on the envelope.

05:15:17 24 MS. WHITT: The password is on the plastic that  
05:15:19 25 the flash drive was in.

05:15:23 1 THE CLERK: This right here?

05:15:25 2 MS. WHITT: Yes, that' right.

05:15:25 3 THE COURT: All right. Is there anything else I  
05:15:27 4 need to address before we recess until tomorrow?

05:15:29 5 Then we'll take earlier recess today.

05:15:32 6 MR. SIPES: Your Honor, I apologize. We did  
05:15:33 7 have one question we just wanted to confirm, which is, the  
05:15:37 8 rule once a witness is sworn, as to whether or not the witness  
05:15:40 9 can talk to counsel until they're sworn for cross or whether  
05:15:45 10 or not the rule goes down as soon as they're sworn for direct.

05:15:49 11 THE COURT: Well, I -- I can tell you my  
05:15:51 12 experience in criminal cases, they always ask me to ensure the  
05:15:55 13 witness does not confer with counsel until the end of  
05:15:57 14 testimony.

05:15:58 15 I haven't had this issue come up in a civil  
05:16:01 16 trial. If there's an objection to counsel talking to  
05:16:04 17 witnesses during their cross-examination --

05:16:07 18 MR. KLEIN: There is certainly an objection to  
05:16:10 19 that. I don't think that's what you --

05:16:12 20 MR. SIPES: No, no, actually either is fine with  
05:16:14 21 me. So I know, in some courts, once a witness is sworn, even  
05:16:18 22 for direct, they can no longer confer with counsel, and in  
05:16:21 23 some courts that bar conferring with counsel does not begin  
05:16:25 24 until their direct ends and the cross starts.

05:16:28 25 I think we've --

05:16:29 1 THE COURT: It would be the latter for me in a  
05:16:31 2 civil case.

05:16:32 3 MR. SIPES: That's fine. That sounds fine with  
05:16:35 4 us, too.

05:16:35 5 MR. KLEIN: That's fine.

05:16:37 6 THE COURT: In terms of the schedule, kind of  
05:16:43 7 what we did today will be how I plan to proceed with a  
05:16:47 8 15-minute break, 15-minute break, and a 30-minute break.

05:16:50 9 I assume you're all setup in the courthouse and  
05:16:53 10 that doesn't create too much inconvenience, and, if so, I  
05:16:56 11 would entertain a request for a longer break if you need it.  
05:17:01 12 But keep in mind the schedule, that I do need to finish by the  
05:17:03 13 end of the month.

05:17:05 14 All right. We'll recess for the day then.

05:17:11 15 (The evening recess was taken.)

05:17:11 16 -o0o-

17  
18 I certify that the foregoing is a correct  
19 transcript from the record of proceedings in the  
20 above-entitled matter.

21 /s/Kathryn M. French  
22 Kathryn M. French, CCR #392, RPR 1/23/2020  
23 Date  
24  
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